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REVIEW

Prevention of non-cavitated lesions with fluoride and xylitol varnishes during orthodontic treatment: a randomized clinical trial

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Abstract

Objective Fixed orthodontic appliances impair oral hygiene increasing the risk of non-cavitated lesions (NCLs) and tooth decay. The aim of this study was to compare the outcomes of fluoride and xylitol varnishes in preventing NCLs during comprehensive orthodontic treatment.

Materials and methods The sample comprised 55 volunteers from 15 to 20 years of age under orthodontic treatment that were randomly divided into three groups: Fluoride Group (FG; *n*=17), Xylitol Group (XG; *n*=19), and Placebo Group (PG; *n*=19). The patients in each group received two applications of the following varnishes: Duraphat™ (5% NaF), 20% xylitol, and placebo (no F/Xylitol) in the three groups, respectively. The varnishes were applied in the first appointment (T0) and 3 months later (T1). Clinical examinations were carried out at T0 and 6 months after (T2) using the ICDAS index and the QLF system (fluorescence difference). The intergroup comparisons were performed by ANOVA/Tukey's or Kruskal-Wallis/Dunn's tests ($P<0.05$).

Results There was no significant intergroup difference regarding ICDAS index changes from T0 to T2. Fluoride varnish produced significantly greater increase in fluorescence of NCLs (mean change of −0.65 ±0.78 and −0.56 ±0.83, for maxilla and mandible, respectively) in comparison to the other groups. The majority of non-cavitated lesions improved in the fluoride and xylitol varnish groups.

Conclusions Fluoride varnish produced significantly greater increase in enamel fluorescence compared to xylitol and placebo varnishes. In short term, both fluoride and xylitol varnishes produced remineralization of NCLs in orthodontic patients.

Clinical relevance Non-cavitated lesions can be effectively controlled in high-risk orthodontic patients by means of fluoride varnishes.

Clinical trial registration ReBEC Identifier: RBR-6mdxfq; Date of Register: March 19th, 2020. Retrospectively Registered

Keywords Dental caries · Fluoride varnish · Xylitol · Orthodontics appliances

Introduction

The Global Burden of Disease Study, in 2016, estimated that half of the world's population have already been affected by an oral disease, and dental caries in permanent teeth was the most prevalent problem [1]. Non-cavitated lesions (NCLs) are associated with a subsuperficial enamel demineralization and represent the first visible stage of dental caries [2, 3]. Factors as oral hygiene routine, dietary habits, fluoride daily exposure, and levels of cariogenic bacteria can have direct effect in caries formation [4]. Recently, Aura-Tormos et al. reported that "Demineralization: prevention and materials" was the 6th most searched topic in Orthodontics [5].

The incidence and prevalence of NCLs in orthodontic patients range from 26 to 97% depending on the diagnostic method [6, 7]. Orthodontic appliances immediately increase

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biofilm formation and *Streptococcus mutans* and *lactobacilli* levels, which has a direct effect on caries formation [8–10]. The risk factors for NCLs formation rapidly increase after appliances installation, having a clinical evolution up to 6 times faster than in patients who do not use braces [6, 11–15]. Additionally, fixed appliances make oral hygiene more difficult [6, 8–14, 16–18]. Previous studies in orthodontic patients showed that preventive strategies can lead to a significant NCLs decrease of 50% in 6 months [19].

The association of different methods, such as water fluoridation, incorporation of fluoride in toothpastes, application of sealants, topical application of varnishes, and oral hygiene guidance with personal responsibility of the patients or their legal guardians, is the key for dental caries prevention [20–22]. An important part of dental practice is to implement strategies according to the patient's individual risk of developing dental caries. The most well-known strategies are constant hygiene orientation and supervision, mouthwash and special toothpaste prescription, and topical application of dental varnish [23].

Fluoride is a gold standard in carious lesion prevention [23–26]. Ten Cate and Buzalaf reported that fluoride in water, toothpastes, and other products are effective [27]. The use of fluoride in the composition of a varnish represent a noncompliance option [20, 28–31]. The American Dental Association (ADA) centre for evidence-based dentistry (2019) recommends the use of 5% sodium fluoride (NaF) varnish applied every 3 to 6 months for treatment of non-cavitated carious lesions. This protocol was not individualized for orthodontic treatment.

Previous studies evaluated xylitol varnish effectiveness as prevention agent [30, 32, 33]. Varnish with 20% xylitol showed relative decrease in *S. mutans* and *S. sobrinus* in the oral biofilm of children when compared to placebo varnish [34]. Recent in vitro and in situ studies revealed that xylitol varnishes were effective in reducing demineralization and accelerating the remineralization of dental enamel [35–37].

Even though promising, xylitol varnish has not been studied neither in vivo nor in orthodontic patients. The aim of this clinical study was to compare xylitol and fluoride varnishes in the prevention/remineralization of NCLs in orthodontic patients. The null hypothesis is that there is no difference in the effectiveness of the two types of varnishes.

Methods

This study was approved by the Ethics in Research Committee of Bauru Dental School, University of São Paulo, Brazil (protocol CAAE – 71639316.0.0000.5417). Written informed consent form was obtained from all volunteers/legal guardians.

This double-blinded randomized clinical trial (RCT) with three-parallel arms was registered in the Clinical Trials Registry (ReBEC) under the identifier #RBR-6mdxfq and followed the Consolidated Standards of Reporting Trials (CONSORT) [38].

The study was conducted from August 2017 to June 2018, and the recruitment occurred at the clinic of Orthodontics at Bauru Dental School, University of São Paulo, Brazil. The inclusion criteria were patients undergoing comprehensive orthodontic, in the level and alignment phase, with pre-adjusted metal brackets (Morelli, Sorocaba, Brazil) treatment 1 to 6 months before study commencement, with 15 to 20 years of age, from both sexes, and with complete permanent dentition. The exclusion criteria were patients with cavitated dental caries, developmental enamel alterations (enamel hypoplasia and fluorosis), and use of antibiotics during the follow-up period.

Outcomes (primary and secondary)

The primary outcomes of this study were the changes in the ICDAS scores in enamel fluorescence (ΔF, in %) assessed with the QLF system. The second outcome is prevalence of new NCLs during the treatment and the percentage of regression in NCLs already stablished.

Sample size calculation

The sample size calculation was performed considering a statistical power of 80%, an α error of 5%, a standard deviation of 0.11 [39], and a minimum difference to be detected in the ICDAS index of 0.5.

Groups and procedures

A randomization was performed by sequenced allocation into 3 groups: Fluoride Group (FG; gold standard, 5% NaF, pH 5.0, Duraphat®, Colgate Palmolive), Xylitol Group (XG; 20% Xylitol, pH 5.0, FGM®), and Placebo Group (PG; synthetic resin base, pH5.0, FGM®). Patients were randomly ordered and sequentially assigned to one intervention group, and the allocation was performed following the order: FG, XG, and PG. The randomization process ensured patients allocation in one of the three groups in a 1:1:1 ratio.

Dental prophylaxis procedure was performed using Robinson brush and Herjos-F toothpaste (412.3ppm of fluoride, Vigodent S/A Rio de Janeiro, Brazil) in all patients at baseline. All patients were submitted to two varnish applications at baseline (T0) and after 3 months (T1). Prior to topical application of the products, the dental surface was air-dried and prepared with relative isolation. A thin layer of the varnish was applied to the dental surface around each bracket with a microbrush. Patients were oriented to avoid drinking or eating up to 2 h after the procedure. All patients at T0 received a

toothbrush, fluoridated toothpaste (COLGATE®, 1,500 ppm of fluoride, Colgate-Palmolive, São Paulo, Brazil), and guidance on oral hygiene. Patients were blinded regarding the type of varnish.

Caries and fluorescence analysis

The variables were assessed at baseline (T0) and 6 months after the first varnish application (T2), as shown in Fig. 1.

Clinical assessment of the buccal surfaces was performed by one trained examiner using the International Caries Detection and Assessment System (ICDAS) [40]. After professional prophylaxis and adequate conditions, the dental surfaces were classified with scores from 0 to 5, in which 0, no visual evidence of NCLs; 1, initial stage of NCLs; 2, distinct visual change in enamel; 3, localized enamel breakdown due to caries without dentine exposure; 4, underlying dark shadow from dentine; and 5, distinct cavity with exposed dentine. Only maxillary and mandibular canines of the skilful side of the patient were used [41].

Quantitative Light-Induced Fluorescence (QLF) images of the buccal surfaces of all premolars and canines of the skilful side of the patient were obtained at T0 and T2 using the Inspektor Pro QLF camera system (Inspektor BV, Amsterdam, The Netherlands). QLF images of T0 and T2 were stored, and each image was independently and blindly analysed by a single examiner using the QLF software (Inspektor Pro 2.0.0.39, Inspektor Research System BV, Amsterdam, The Netherlands). The images in T0 and T2 were adjusted in the same position before calculating the surface fluorescence (ΔF, in %, Fig. 2) and caries lesion volume (ΔQ, in % mm^2).

ICDAS and QLF assessments examiner was unaware of the patient's group.

Error study

The measurements were repeated by the first author using 30% of the QLF images with an interval of at least 1 month. Reproducibility of the ICDAS scores was evaluated using Kappa index after re-evaluation of 30% of the sample after 30 days. The intra-rater reliability regarding surface fluorescence was assessed using intraclass correlation coefficient (ICC).

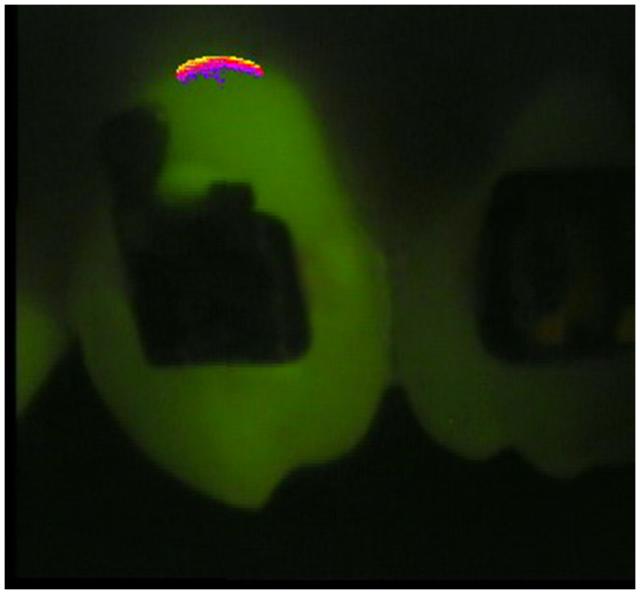

Fig. 2 Surface reading with the QLF system at the left inner first premolar

Statistical analysis

Data normality and homogeneity were respectively assessed by Kolmogorov-Smirnov and Bartlett's tests. Intergroup comparability regarding initial age and sex distribution were evaluated with ANOVA and Chi-square tests, respectively (Table 1). Baseline intergroup comparison was analysed using ANOVA and Kruskal-Wallis tests. Intergroup differences for changes in caries index and enamel fluorescence were evaluated using ANOVA/Tukey's or Kruskal-Wallis/Dunn's tests for variables with normal or non-normal distributions, respectively. The statistical analyses were performed using Statistica software (Statistica for Windows version 11.0; StatSoft, Tulsa, Okla) with a significance level of 5%.

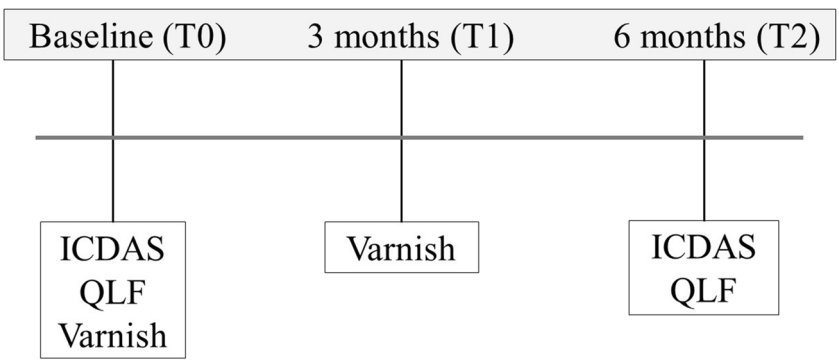

Fig. 1 Study design

Table 1 Intergroup comparisons for age and sex distribution (ANOVA and Chi-square tests)

Variables	FG (*n*=17)		XG (*n*=19)		PG (*n*=19)		*p*
	Mean (SD)	Cl 95%	Mean (SD)	Cl 95%	Mean (SD)	Cl 95%	
Initial age (y)	15.6 (1.8)	14.7–16.6	14.1 (2.0)	13.2–15.1	15.0 (2.0)	14.0–15.9	0.081[§]
Sex							
Male	09		08		09		0.809[ˈ]
Female	08		11		10		

Cl confidence interval, *SD* standard deviation, *y* years, *FG* Fluoride Group, *XG* Xylitol Group, *PG* Placebo Group

[§] Anova test

ˈChi-square test

Results

During the study period, 70 patients were examined. Sixty volunteers were enrolled according to the eligibility criteria and randomized in a 1:1:1 ratio to the three study groups (FG= 20, XG=20, and PG=20). Five patients were lost during follow-up, 3 in the FG (15%), 1 in the XG (5%), and 1 in the PG (5%). The excluded patients had their orthodontic fixed appliances removed before T2 analyses or did not attend the appointments. Fifty-five patients were properly analysed. Therefore, since the ICDAS analysed only the canines of the skilful side of the patients, 55 teeth were analysed. Because the QLF analysed canines and premolars of the skilful side, 110 teeth were analysed. Figure 3 shows the participants flow chart. No difference was found in the baseline comparisons for all variables, except for the F mandible, that presented a difference between GF and GP (Table 2).

The intra-examiner Kappa index for the ICDAS scores was strong (≥ 0.9). The intra-examiner reliability for ΔF was strong with the ICC ranging from 0.997 to 0.999.

The study groups were similar regarding age and sex distribution at baseline (Table 1).

No significant intergroup differences were observed in the ICDAS index and ΔQ (lesion volume) changes (Table 3). The fluorescence assessment indicated an improvement in the dental surface mineralization in all study groups. The fluoride varnish (FG) showed a greater increase of enamel mineralization than xylitol and placebo varnish, respectively, for the maxillary and mandibular teeth.

Only 19% of the 110 analysed teeth had non-cavitated lesions. The FG had 9 teeth with NCLs, the XG had 7, and the PG had 5. In the FG group, 6 (67%) of the teeth with NCLs regressed, but another tooth showed a NCLs at the end. In the XG, 7 (100%) of the teeth with NCLs regressed, but another tooth showed a NCLs at the end. In the PG, none of the lesions were regressed (Table 4).

Discussion

This is the first clinical study comparing xylitol and fluoride varnishes in orthodontic patients. The Kappa index for ICDAS was adequate, and the surface fluorescence variables presented excellent intra-examiner agreement. Previous studies also demonstrated adequate reproducibility for the ICDAS with Kappa index varying from 0.59 to 0.82 [33, 36, 40, 42–44]. The QLF system consists of an image analyses which can calculate the percentage of fluorescence loss of the selected enamel area based on the amount of mineral loss during the analysed period. Benson et al. (2003) also showed a strong reproducibility of the method and validated the QLF system [45, 46].

Among the different available exams for caries detection, both methods used in this study were proven to have similar performance compared to histological gold standard scores for caries detection [47, 48]. The QLF system was chosen due to its sensitivity and efficiency [6, 49, 50]. This exam is capable of recording a minor area of demineralization during orthodontic treatment with a 5% fluorescence loss detection, value that is not possible to be detected in a visual and clinical examination [6]. The clinical exam, ICDAS, was developed to analyse changes in the enamel surface related to the potential histological status of the lesion [43]. This visual exam depends on a previous examiner calibration, and it is popularly used due its excellent sensitivity, accessibility, and practical use. ICDAS index showed good accuracy, especially in lesions located in the superficial layers of the enamel [51]. Both technique limitations are that they can be affected by inadequate prophylaxis, illumination, and dryness of the examined surface, as well as resin excess and inflammatory and bleeding status of the gingiva.

Orthodontic patients have a high risk of caries formation, and its incidence is higher in canines and premolars, having a clinical evolution 6 times faster than in non-orthodontic patients [40, 41]. Safety, efficacy, simple application, frequency, and patient acceptance are all factors that can affect the election of the preventive strategy. Individual compliance ensuring adequate oral hygiene is still a challenge for orthodontic patients, which lead clinical orthodontists to use associated methods, as the topical application of varnishes.

In the present study, we enrolled 55 15–20-year-old volunteers under orthodontic treatment that were randomly assigned into 3 different groups, according to the varnishes that were

Table 2 Baseline intergroup comparisons for all variables (ANOVA and Kruskal-Wallis)

ICDAS												
Variables	FG (*n*=17)				FG (*n*=19)				PG (*n*=19)				*p*
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	
ICDAS maxilla¥	0.47 (0.79)	0 (0/1)	0	2	0.10 (0.31)	0 (0/0)	0	1	0.21 (0.53)	0 (0/0)	0	2	0.267
ICDAS mandible¥	0.41 (0.79)	0 (0/0.5)	0	2	0.36 (0.68)	0(0/1)	0	2	0.15 (0.50)	0 (0/0)	0	2	0.445
F (degree of fluorescence—in %)													
Variables	FG (*n*=34)				FG (*n*=38)				PG (*n*=38)				*p*
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	
F maxilla§	−8.01 (0.86)	−7.84 (−8.63/−7.66)	−10.53	−6.71	−7.49 (0.71)	−7.28 (−8.16/−6.97)	−8.94	−6.42	−7.51 (0.39)	−7.50 (−7.83/−7.29)	−8.14	−6.52	0.163
F mandible§	-8.08^{A} (0.56)	−8.08 (−8.27/−7.86)	−9.11	−7.16	-7.81^{AB} (0.56)	−7.87 (−8.13/−7.41)	−8.68	−6.64	-7.59^{B} (0.68)	−7.43 (−7.79/−7.26)	−9.15	−6.64	0.007*
Q													
Variables	FG (*n*=17)				FG (*n*=19)				PG (*n*=19)				*p*
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	
ICDAS maxilla¥	−1.43 (0.92)	−1.24 (−2.15/−0.61)	−3.20	−0.27	−0.91 (0.59)	−0.79 (−1.17/−0.52)	−2.37	−0.10	−1.17 (0.84)	−0.79 (−2.02/−0.36)	−2.84	−0.17	0.246
ICDAS mandible¥	−1.80 (1.07)	−1.50 (−2.70−/−0.98)	−4.34	−0.39	−1.40 (1.61)	−0.73 (−1.98/−0.36)	−6.78	−0.09	−1.18 (0.69)	−1.05 (−1.73/−0.63)	−2.87	−0.21	0.138

FG Fluoride Group, *XG* Xylitol Group, *PG* Placebo Group, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

§ Anova

¥ Kruskal-Wallis

*Statistically significant at $P<0.05$

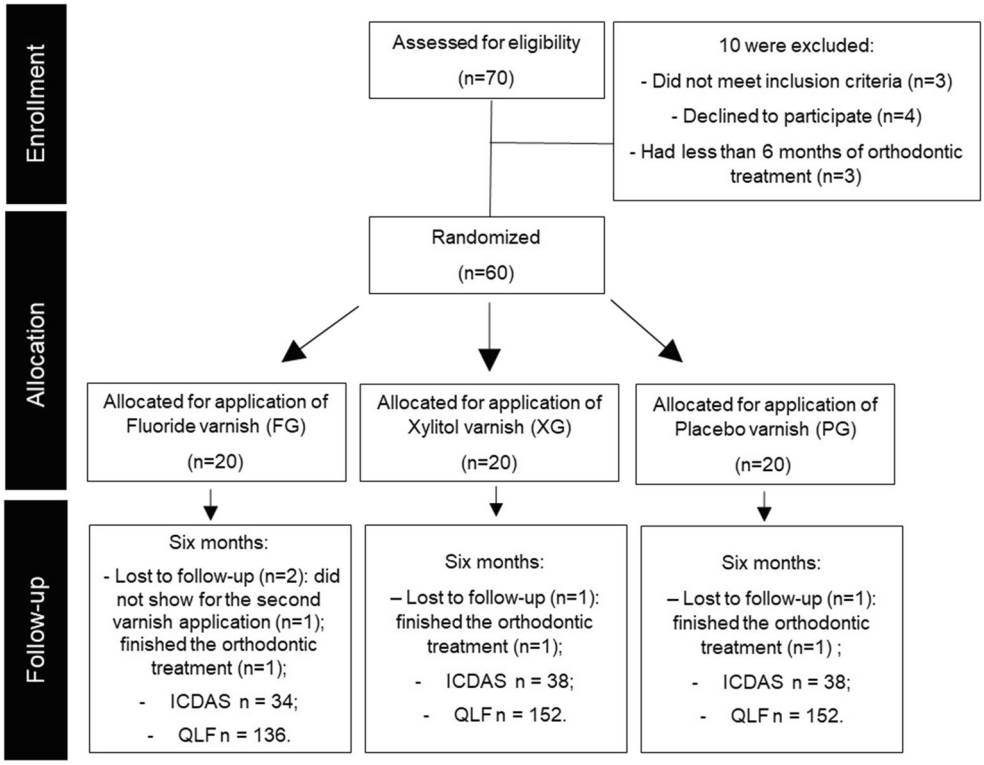

Fig. 3 Participants flow chart with losses and exclusions

applied on their teeth. No difference was found in the baseline comparisons for the variables evaluated, except for the F mandible. In this case, GF presented a higher value than GP, which denotes a higher degree of demineralization.

There were no significant differences on the enamel surface changes from T0 to T2 using the ICDAS index among the three groups (Table 3). This result corroborates with a previous study [52]. Both study and control groups presented low frequency of non-cavitated lesions in T0 and T2, probably due to the presence of fluoride in the toothpaste, water distribution, and constant hygiene stimulation during the orthodontic appointments [42].

On the other hand, fluorescence assessment (QLF) of the enamel indicated that 6 months was enough to obtain improvement of the dental surface mineralization (Table 3). Gokce et al. showed in an in vitro study that only 2 weeks was enough to observe statistical differences in the QLF analyses [53]. Fluoride varnish (FG) showed greater increases of enamel mineralization compared to xylitol and placebo varnishes, in the maxillary and mandibular teeth, respectively. The fluorescence difference between FG and PG in the mandible might be explained by the presence of fluoride in the FG group. This is not surprising, since the pooled D(M)FS prevented fraction estimate comparing fluoride varnish with placebo is estimated to be 43% [32]. It is important to highlight that the FG presented a significantly higher degree of fluorescence (F) loss at baseline as compared with PG, which means that the degree of remineralization was higher than the value expressed by the ΔF.

At T2, the FG group had lesion regression in 67% of the teeth that initially presented NCLs, the XG had lesion regression in 100%, and the PG had no teeth with regression. Considering the regression of the lesions in each group, fluoride and xylitol varnishes were both able to mineralize non-cavitated lesions. Consequently, xylitol varnishes seem to be an alternative to fluoride varnishes in NCLs prevention and remineralization during orthodontic treatment. However, future clinical studies with a longer observation period should be performed. A limitation of the present study was the short evaluation period of 6 months. Future studies should compare fluoride and xylitol varnishes for longer periods of at least 1-year period.

Conclusions

- Fluoride varnish produced significantly greater increase in enamel fluorescence compared to xylitol and placebo varnishes;
- In the short term, both fluoride and xylitol varnishes produced remineralization of non-cavitated lesions in orthodontic patients.

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Table 3 ICDAS score changes (T0–T2) and fluorescence variation (ΔF) assessed by ANOVA/Tukey's or Kruskal-Wallis/Dunn's tests

ICDAS													
Variables	FG (*n*=17)				XG (*n*=19)				PG (*n*=19)				
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	*p*
ICDAS maxilla¥	0.12 (0.33)	0 (0–0)	0	1	0.00 (0.00)	0 (0–0)	0	0	0.00 (0.00)	0 (0–0)	0	0	0.102
ICDAS mandible¥	0.00 (0.35)	0 (0–0)	−1	1	0.00 (0.33)	0 (0–0)	−1	1	0.00 (0.00)	0 (0–0)	0	0	1.000
ΔF (%)													
Variables	FG (*n*=34)				FG (*n*=38)				PG (*n*=38)				
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	*p*
ΔF maxilla§	−0.65(0.78)^{A}	−0.64 (−1.01/−0.80)	−2.47	0.44	−0.08 (0.63)^{B}	−0.11 (−0.28/0.23)	−1.38	1.20	−0.21 (0.64)^{AB}	−0.32 (−0.56/0.01)	−1.23	−1.00	0.044*
ΔF mandible§	−0.56 (0.83)^{A}	−0.50 (−0.80/−0.09)	−2.67	0.50	−0.15 (0.62)^{AB}	−0.31 (−0.59/−0.07)	−0.91	1.36	0.05 (0.56)^{B}	0.07 (−0.28/0.32)	1.27	1.43	0.031*
ΔQ (%)													
Variables	FG (*n*=34)				FG (*n*=38)				PG (*n*=38)				
	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	Mean (SD)	Median (Q1/Q3)	Min	Max	*p*
ΔF maxilla¥	−0.52 (1.06)	0.44 (−0.54/1.40)	−1.03	2.53	0.25 (0.60)	0.21 (−0.16/0.45)	−0.70	1.92	0.57 (0.70)	0.41 (0.09/1.13)	−0.86	1.84	0.400
ΔF mandible¥	0.76 (1.15)	0.80 (0.02/1.32)	−0.83	3.99	0.46 (1.19)	0.26 (−0.05/0.83)	−1.32	3.58	0.34 (0.84)	0.44 (−0.15/0.72)	−1.33	2.51	0.386

FG Fluoride Group, *XG* Xylitol Group, *PG* Placebo Group, *Q1* first quartile, *Q3* third quartile, *SD* standard deviation

§ Anova

¥ Kruskal-Wallis

*Statistically significant at $P<0.05$

Table 4 Number of activity and inactivity non-cavitated lesions in T0 and T2 time-points

Follow-up	FG (*n* = 17)		XG (*n*=19)		PG (*n*=19)	
	Inactive	Active	Inactive	Active	Inactive	Active
T0	0	9	0	7	0	5
T2	5	4	6	1	0	5

FG Fluoride Group, *XG* Xylitol Group, *PG* Placebo Group

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Vinicius Merino da Silva, Camila Massaro, Guilherme Janson, and Daniela Garib. Varnish selection and ICDAS and QLF analyses were performed by Vinicius Merino da Silva, Camila Massaro, Marilia Afonso Rabelo Buzalaf, and Daniela Garib. The first draft of the manuscript was written by Vinicius Merino da Silva, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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

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

Conflict of interest The authors declare no competing interests.

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