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Randomized Controlled Trial

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Evaluation of the preventive effect of two concentrations of xylitol varnish versus fluoride varnish on enamel demineralization around orthodontic brackets: a randomized controlled trial

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Summary

Background: The highly prevalent white spot lesions around orthodontic brackets necessitate introducing preventive materials without relying on patient compliance.
Objective: To evaluate the antidemineralizing effect of two concentrations of xylitol varnish.
Trial design: Triple-blind, four-arm, parallel-group, single-center, randomized controlled clinical trial.
Methods: A total of 120 orthodontic patients were randomly assigned to four groups (n = 30), using a computer-generated randomized block list. The treatment groups were: 10% xylitol, 20% xylitol, 5% fluoride, and placebo. Tooth demineralization was measured with DIAGNOdent at T_1 (before treatment), followed by varnish application. At T_2 (third month), the varnish was re-applied, and at the third (T_2) and sixth (T_3) months, and after treatment (T_4), the demineralization was measured. The white spot lesion frequency was assessed visually after treatment. The participants, the clinician, and data assessors were all blinded to group assignments.
Results: A total of 115 patients underwent per-protocol analyses. At T_2, the mean DIAGNOdent numbers in the fluoride and 10% xylitol groups were significantly lower than the placebo group (P = 0.00), with a mean difference of 0.63 (95% CI, 0.15–1.10) and 0.5 (95% CI, 0.04–0.95), respectively. At T_3, the fluoride and 10% xylitol groups had significantly lower mineral loss than the placebo group (P=0.046) with a mean difference of 0.52 (95% CI, 0.14–0.89) in the fluoride and 0.45 (95% CI, 0.03–0.86) in the 10% xylitol groups, respectively. However, at T_4, only the mean for the 10% xylitol group was significantly different (P=0.049) from the placebo group, with a mean difference of 1.18 (95% CI, 0.42–1.93). Visual assessment showed that after treatment, the prevalence of white spot lesions in the fluoride (P=0.03) and 10% xylitol (P=0.00) groups was less than the placebo group with the odds ratio of 0.67 (95% CI, 0.46–0.96) and 0.43 (95% CI, 0.28–0.64), respectively.
Conclusion: The 10% xylitol varnish short-term effects on caries control were significantly greater than 20% xylitol varnish and placebo but similar to fluoride varnish. However, the 10% xylitol long-term effect was almost better than fluoride varnish.
Trial registration: The protocol was registered at IRCT.ir under the code IRCT20180913041032N1.

Introduction

One of the most severe problems facing orthodontists is enamel demineralization and white spot lesion formation around orthodontic brackets, which have an adverse effect on tooth health and, more importantly, on aesthetics (1). White spot lesions (WSLs) can develop after four weeks of treatment, and their incidence has been estimated up to 50% (2). This high incidence is due to retention sites of orthodontic appliances that facilitate bacterial aggregation and biofilm formation (3). Also, it has been shown that resin-bonded materials around brackets are more prone to bacterial adhesion than the enamel (4).

Several anticariogenic agents have been used to prevent dental caries to date, such as fluoride, chlorhexidine, and xylitol (5). Xylitol is a natural sugar alcohol available in different commercial forms like chewing gums, dental wipes, oral syrups, lozenges, mouthwashes, toothpastes, and candies (6). The preventive role of xylitol products in dental caries has been shown in several studies (7–11). However, some studies in orthodontics have revealed that *S. mutans* counts remain unchanged after using xylitol products (12–14).

A high frequency of xylitol intake has been reported to be important in caries prevention (15). Considering this protocol, vehicles (e.g. chewing gums, tablets, candies, etc.) must be used several times every day, which requires patient compliance and could cause discomfort for the patient (16). Therefore, a xylitol regimen that does not require patient compliance would be a better alternative to protect against dental caries (9, 16, 17). Taking this into account, recently, attempts have been made to include xylitol into a varnish formulation that provides sustained release of xylitol due to the long-term adhesion to the enamel surface. Moreover, it does not require patient compliance (18–21). Pereira *et al.* (18) made the first attempt to produce xylitol-containing varnishes and reported increased xylitol levels in the saliva after applying 20% xylitol varnish on a short-term basis. However, 10% xylitol was shown to have sustained release and, therefore, to be more effective in increasing the xylitol level in the saliva over a long period. In two studies by Cardoso *et al.* (20, 21), the remineralization effect of xylitol varnish was investigated, and the highest decrease in lesion depth was found when 20% xylitol varnish was used compared to 10% xylitol, fluoride, and a combination of varnishes. Besides, they showed that a combination of xylitol and fluoride was ineffective in improving remineralization.

The anticariogenic effect of xylitol products has been shown in preventive dentistry (7–11), and in orthodontic patients, the effects of xylitol gums and tablets on *S. mutans* counts (12–14, 22) have been evaluated so far. A few in situ and in vitro studies and one clinical study have investigated the xylitol varnish (19–21, 23) regarding its effect on the remineralization of carious lesions. However, to the best of our knowledge, no studies have evaluated the long-term effects of different concentrations of xylitol varnish in preventing demineralization and early enamel carious lesions around orthodontic brackets in the clinic to date.

Specific objective and hypothesis

This study aimed to evaluate the in vivo effect of topical xylitol varnish application with 10% and 20% concentrations on preventing enamel demineralization adjacent to orthodontic brackets in comparison with fluoride and placebo varnishes over the orthodontic treatment period. The null hypothesis was that the four groups have the same effect on demineralization around orthodontic brackets.

Methods

Trial design

This study was a single-center, triple-blind, four-arm, parallel-group, and active randomized trial design, with 1:1:1:1 ratio. Two groups received the experimental materials, and two groups served as positive and negative control (fluoride varnish and placebo) groups. No changes were made to the methods after initiating the trial.

Participants, eligibility criteria, and setting

The subjects were selected from patients 12–20 years of age, requiring fixed orthodontic treatment in a public dental clinic in Shiraz, Iran. All the patients included in this trial were treated by one orthodontist (HZN), who was blinded regarding the interventions. Informed consent was obtained before the final enrollment. The study was approved by the local ethics committee (code: IR.SUMS.REC.1397.413).

The inclusion criteria consisted of patients with complete permanent dentition up to the first molars, good overall health, and good oral hygiene (a full-mouth plaque score of <20%); no bleeding upon probing after 30 seconds, or a discontinuous band of plaque at the gingival margin, normal stimulated salivary flow rate (>1.0 mL/min) and buffer capacity (a final pH of 6.0 and 7.0). Patients were excluded if they exhibited the following: a history of previous orthodontic treatment or extraction, bleaching or topical fluoridation within the last six months, severe crowding of >6 mm, necessitating extraction of teeth, severely rotated teeth, visible signs of caries, fluorosis, hypocalcification or developmental defects, dental crowns, amalgam or composite filling extending to the buccal surface, a systemic or endocrine condition (such as cardiac pacemakers or diabetes mellitus), craniofacial anomalies, and clefts, and smokers.

Randomization and allocation concealment

All the participants were randomized using a dynamic randomized block design for balancing age and gender. A block randomization list was created by https://www.sealedenvelope.com with a block size of eight. Block randomization minimizes the imbalance over multiple significant baseline covariates between treatment arms for all the allocations within and between blocks (24). The group allocation was carried out by an assistant not directly involved in the study only after each patient was seated for the initial bonding appointment, and a random numerical code was assigned to each patient at the beginning of the study based on the randomization list created before.

Intervention

The patients assigned to four groups consisted of subjects receiving 10% xylitol varnish, 20% xylitol varnish, 5% fluoride varnish, and placebo varnish.

Xylitol and placebo varnishes were specially manufactured by the Asia ChemiTeb Co. (Tehran, Iran) with the same basic composition as the commercial Ariadent fluoride varnish (Asia ChemiTeb Co., Tehran, Iran).

Two weeks before the bonding session, all the patients attended a specialized scaling, debridement, and polishing session and received standard oral hygiene instructions on tooth brushing twice a day and flossing every day by a dental hygienist not involved in the study. An orthodontic kit (GUM Sunstar, Americas, Chicago, USA) containing an orthodontic toothbrush, proximal brush, thread floss, orthodontic wax, and a tube of fluoride toothpaste (1450 ppm fluoride, Colgate, USA) was given to all the participants who were asked to use only toothpaste and floss given to them. At each visit, patients brought their toothbrushes, floss, and toothpaste to be reminded of oral hygiene instructions if needed and received new toothpaste and floss if necessary.

Primary outcome: fluorescence assessment

In the bonding appointment, the subjects' teeth up to the first molars (first molars were banded and not included in the assessments) were cleaned with a pumice stone and a brush mounted on a low-speed contra-angle handpiece (NSK, Kanuma, Japan), dried with an air syringe, and isolated with cotton rolls. Enamel mineralization of the teeth was measured with a DIAGNOdent Pen 2190 (KaVo, Biberach und der Riss, Germany). The laser was calibrated for each patient according to the manufacturer's guidelines. The teeth were scanned carefully by the same dentist who was blinded to group allocations of the subjects using a probe tip B held in contact with the tooth surface and tilted around the measuring site, rocking slowly in a pendulous motion. Therefore, the fluorescence could be collected from all directions at four labial sites on the enamel (gingival, occlusal, mesial, and distal), as suggested by Banks and Richmond (25).

Before bonding, the four sites on the labial surface of each tooth were determined approximately based on the imaginary bracket positioned at the FA point. The maximum reading displayed on the panel of the DIAGNOdent pen during the scanning was recorded for each tooth site, and then the mean value for each tooth was recorded as initial values (T_1) in the patients' dental records.

After that, orthodontic brackets (Mini Master Series, American Orthodontics, Sheboygan, Wisconsin, USA) were bonded to the teeth with Transbond XT adhesive (3M Unitek, Monrovia, California, USA). The dental arches were isolated and dried, and then the varnish was applied on the buccal surface surrounding the bracket using a microbrush. After about five minutes of setting time, the patient was asked to refrain from eating or drinking for four hours and not brush the experimental teeth for six hours, based on the manufacturer's recommendations.

The fluorescence assessment was performed by the DIAGNOdent Pen 2190, which contains a diode laser with a wavelength of 655 nm and a power of <1 mW. According to the literature, the DIAGNOdent has excellent specificity and accuracy, similar to visual and tactile examinations and radiography (26–28). The DIAGNOdent Pen 2190 measures the fluorescence emitted by the tooth in response to irradiation at a specific wavelength. In each group, the efficacy of antidemineralizing agents was assessed three (T_2) and six months (T_3) after the initiation of orthodontic treatment and at the end of orthodontic treatment (T_4). In follow-up visits, mineralization of the enamel was measured as follows: the vestibular surfaces of all the teeth were cleaned using a brush mounted on a low-speed contra-angle handpiece (NSK, Kanuma, Japan), and the residual varnish was removed to prevent it from being read as a false positive result. The fluorescence was emitted at four sites, each 1 mm away from the bracket using the DIAGNOdent Pen 2190. Then the varnish was re-applied to all the teeth in each group at the T_2 time interval. At the T_3 and T_4 time intervals, the DIAGNOdent score was checked without re-applying the varnish. The average DIAGNOdent values of all the teeth were calculated, and a mean value was reported for each patient. No changes in the trial outcomes occurred after the trial commenced.

Secondary outcomes

Visual assessment

Since the patients who had a visible sign of caries and hypocalcification were not included in this study, the visual assessment of white spot lesions was performed at the end of orthodontic treatment. After removing orthodontic appliances, the remnant adhesive was removed with a tungsten carbide bur (Dentaurum no.123–604, Ispringen, Germany) at low speed, followed by polishing with a rubber cup and non-fluoride pumice paste. To assess the presence of white spot lesions, the labial surface of maxillary anterior teeth, including first and second premolars (A total of 10 teeth), was air-dried for 10 seconds. The severity of white spot lesions was recorded according to the Gorelick index (score 0: no visible white spot, score 1: visible WSL that covered less than one-third of the surface, score 2: visible WSL that covered more than one-third of the surface, score 3: visible cavitation) (29).

To measure intra-rater reliability, 24 patients were selected randomly to reassess their teeth one week after the first evaluation. The agreement of two assessments measured through Cohen's kappa coefficient was strong, with a value of 88%.

Adverse effect and patients' satisfaction

The patients' opinion about varnish therapy was evaluated by a yes/no questionnaire comprising six questions: 1. feeling nervous at varnish therapy appointments, 2. feeling unhappy about appointment length, 3. noticing a temporary color change in teeth after varnish therapy, 4. satisfaction with taste and smell, 5. gastrointestinal symptoms after varnish therapy, and 6. the overall satisfaction.

Sample size calculation

The sample size was calculated with an assumed detectable difference of 1.5 in mean DIAGNOdent readings, with a standard deviation of 2.0 (30), a significance level of 0.05, and a power of 80%. The sample size was estimated at 27 patients in each group. Due to possible drop-outs, 120 patients (n = 30 in each group) were enrolled in this study.

Interim analyses and stopping guidelines

No interim analyses were applied, and no stopping guidelines were employed in this trial.

Blinding

The patients, therapists, and the data assessors were blinded to the type of varnish used. In this regard, the varnish bottles' shapes were similar and labeled as A, B, C, or D randomly by a person not involved in this study.

Statistical analysis

The data were statistically analysed using SPSS 20 (Statistical Packages for the Social Sciences, Chicago, IL). To evaluate the distribution of patients in each group regarding gender and age, chi-squared and Kruskal–Wallis tests were used, respectively. The treatment durations were compared between the groups using ANOVA. The mean of DIAGNOdent readings for each patient was subjected to statistical analysis and compared within groups at different time intervals (baseline, three months, six months, and at the end at orthodontic treatment) using the Friedman test. Also, Kruskal–Wallis test was used for detecting intergroup differences at each time interval. Then the Dunn's test (already built-in within SPSS as a pairwise comparison) was applied as a *post hoc* subgroup analysis.

The frequency of WSLs after orthodontic treatment was categorized by the chi-squared test. Then, the odds ratio of WSLs formation was calculated using binary logistic regression analysis.

Results

The participants' flow diagram

A total of 120 patients were enrolled in this study for intervention from November 2018 to Jun 2019. The follow-up process started from February 2019 to December 2019. A CONSORT flow diagram of the enrolment, intervention allocation, follow-up, and data analysis process is presented in Figure 1. Five patients did not attend their follow-up appointments on schedule and were excluded from the per-protocol analyses. All 120 patients were included in intention-to-treat (ITT) analysis at T4. Because uncooperative patients only received the varnish therapy at the start of orthodontic treatment and did not regularly attend follow-up sessions, it was not possible to take records at T2 and T3; but, they were included in the final ITT analysis.

Baseline data

The demographic characteristics of the participants regarding gender and age are presented in Table 1. No significant difference was found in the distribution of patients between the groups regarding gender and age (P=0.85 and P=0.69), implying proper randomization of the patients. Furthermore, the duration of orthodontic treatment was the same in four groups (mean: 18.7±3.5, P=0.80).

Primary outcome

The mean values of DIAGNOdent numbers for each group at different time intervals based on per-protocol analysis are presented in Table 2. The results showed that in all the groups, the DIAGNOdent readings increased significantly (P<0.0001) from T_1 to T_4 based on both ITT and per-protocol analysis (Figure 2).

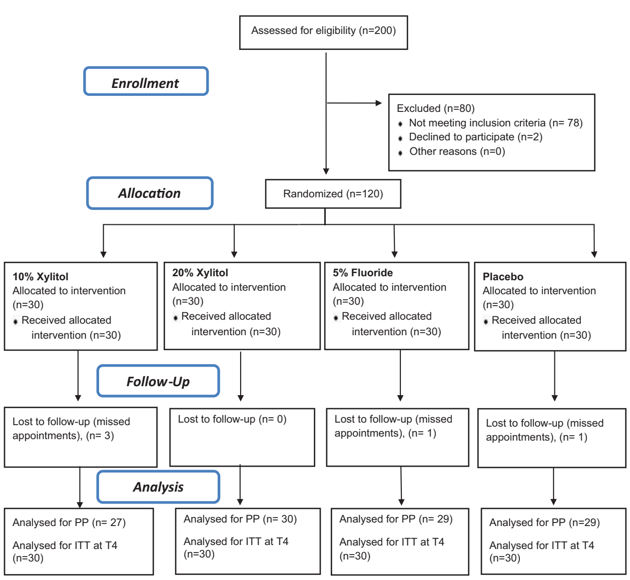

Figure 1. CONSORT flow diagram of the study recruitment.

At all the follow-up appointments, statistically significant differences were found between the study groups regarding DIAGNOdent numbers according to per-protocol analysis (Table 2).

At T_2 and T_3, the mean of DIAGNOdent readings in both the fluoride and 10% xylitol groups were significantly lower than the placebo group. At T_2, the mean difference in fluoride and 10% xylitol group was 0.63 (95% CI, 0.15–1.10, P=0.020) and 0.5 (95% CI, 0.04–0.95, P=0.043); and at T_3 the mean difference in fluoride and 10% xylitol group was 0.52 (95% CI, 0.14–0.89, P=0.024) and 0.45 (95% CI, 0.03–0.86, P=0.039), respectively. At T_4, the only group in which the mean of the DIAGNOdent readings was different from that of placebo was 10% xylitol (P=0.046). On the other hand, no significant difference was found between 20% xylitol and placebo at any time.

The results of ITT analysis at T_1 and T_4 are also presented in Table 3. No significant difference was found between groups at these two time intervals (P=0.86 and P=0.092, respectively).

Secondary outcome

Visual assessment

The labial surface of 1150 and 1200 teeth was evaluated visually according to per-protocol and ITT analysis, respectively. Chi-squared test was applied to compare the differences in the distribution of white spot lesions between the four treatment groups and the difference was significant (P=0.000). As it is shown, the advanced lesions are more prevalent in the 20% xylitol and placebo groups. The presence of WSLs (considering the Gorelick index of 1, 2, and 3) was significantly lower in the 5% fluoride and 10% xylitol groups compared to the placebo group both in ITT and per-protocol analysis (Table 4).

The odds ratio in the fluoride group based on the per-protocol and ITT analyses was 0.67 (95% CI, 0.46–0.96 and 0.47–0.97), with 0.43 (95% CI, 0.28–0.64) and 0.55 (95% CI, 0.38–0.80) in the 10% xylitol group, respectively.

Adverse effect and patient satisfaction

Of 115 patients included in this study, according to the per-protocol analysis, one patient felt nervous at intervention appointments, and two felt unhappy about the appointment length. No gastrointestinal symptoms and no dissatisfaction with taste and smell were reported. Nine patients noticed a temporary change in the color of their teeth after varnish therapy, four of whom were in the 20% xylitol group. In general, three patients were not satisfied with the overall treatment.

Harms

No harm was observed during the trial.

Discussion

The idea of incorporating xylitol into a varnish, a vehicle that assures sustained release of xylitol without patient cooperation, was first conceived by Pereira *et al.* (18) in 2012. Two concentrations of xylitol varnish have been shown to be effective in caries control so far in vitro: 10% and 20% (21, 31).

In this parallel-group randomized clinical trial, the focus was directed on the preventive effect of xylitol varnish with different concentrations (10% and 20%) compared to 5% fluoride varnish and placebo varnish at two follow-up visits with a three-month interval and the end of orthodontic treatment.

Table 1. The demographic characteristics of the participants included in the per-protocol analysis.

	Total (*n* = 115)	10% Xylitol (*n* = 27)	20% Xylitol (*n* = 30)	5% Fluoride (*n* = 29)	Placebo (*n* = 29)	*P*-value
Age (mean ± SD)	15.9 ± 3.5	16.1 ± 3.8	16.50 ± 3.8	15.7 ± 2.6	15.4 ± 3.7	0.69
Female, no. (%)	62 (53.9)	15 (55.6)	17 (56.7)	16 (55.2)	14 (48.2)	0.85
Male, no. (%)	53 (46.0)	12 (44.4)	13 (43.3)	13 (44.8)	15 (51.8)	
Treatment duration (mean ± SD)	18.7 ± 3.5	19.3 ± 3.6	18.2 ± 3.4	18.8 ± 3.9	18.6 ± 3.3	0.80

Table 2. Comparison of DIAGNOdent numbers of each group at different time intervals based on the per-protocol analysis (T_1: before the intervention, T_2: third month of treatment, T_3: sixth month of treatment, T4: at the end of treatment).

Time	Intervention	No.	Mean (±SD)	CIs	*P*-value	*P*-values versus placebo group
T_1	10% Xylitol	27	1.20 (±0.74)	0.82–1.58		0.979
	20% Xylitol	30	1.10 (±0.88)	0.69–1.51	0.753	1.000
	5% Fluoride	29	1.09 (±0.89)	0.66–1.53		1.000
	Placebo	29	1.10 (±1.05)	0.60–1.61		
	Total	115	1.12 (±0.88)	0.92–1.33		
T_2	10% Xylitol[a]	27	1.29 (±0.48)	1.05–1.54		0.043*
	20% Xylitol[b]	30	1.94 (±0.78)	1.57–2.31	0.005*	0.334
	5% Fluoride[a]	29	1.16 (±0.66)	0.85–1.48		0.020*
	Placebo[b]	29	1.79 (±1.09)	1.26–2.32		
	Total	115	1.56 (±0.84)	1.36–1.75		
T_3	10% Xylitol[a]	27	1.30 (±0.63)	0.97–1.63		0.039*
	20% Xylitol[b]	30	1.73 (±0.76)	1.37–2.09	0.046*	0.937
	5% Fluoride[a]	29	1.23 (±0.45)	1.01–1.45		0.024*
	Placebo[b]	29	1.78 (±0.90)	1.34–2.22		
	Total	115	1.52 (±0.74)	1.35–1.69		
T_4	10% Xylitol[a]	27	3.12 (±1.17)	2.51–3.72		0.046*
	20% Xylitol[b]	30	4.27 (±1.62)	3.51–5.03	0.049*	1.000
	5% Fluoride[a,b]	29	3.47 (±1.44)	2.78–4.17		0.213
	Placebo[b]	29	4.30 (±1.59)	3.53–5.07		
	Total	115	3.81 (±1.53)	3.46–4.17		

[a,b]Different letters indicate a significant statistical difference in the pairwise analysis.
*$P<0.05$ (Kruskal-Wallis test).

From the beginning of orthodontic treatment to its end, an increase in demineralization was observed in all the groups, especially in the last period when varnish therapy was not performed.

Increasing the rate of mineral loss shortly after the beginning of orthodontic treatment (32–34) and control of the progression of demineralization by fluoride varnish during orthodontic treatment was shown in previous studies (35–37), consistent with our results. At follow-up visits at T_2 and T_3, a comparison of mineral loss of all the four groups showed that 5% fluoride and 10% xylitol had a similar effect and were more effective in preventing demineralization than placebo and 20% xylitol. However, at the end of orthodontic treatment, only the 10% xylitol group showed marginally lower mineral loss comparing the others groups (*P*=0.049), indicating the small long-term beneficial effect of 10% xylitol.

The visual assessment of white spot lesions at the end of orthodontic treatment almost conformed to DIAGNOdent readings. Our result showed that both fluoride and 10% xylitol varnish had a long-term protective effect on white spot lesion formation, and 10% xylitol varnish was slightly more effective than fluoride varnish.

It should be noted that the results of both DIAGNOdent readings and visual assessments for the 10% xylitol group, according to per-protocol analysis, were slightly better than ITT analysis. It can be due to excluding patients with poor cooperation from this group. These patients received varnish only at the beginning of treatment.

The long-term effect of fluoride varnish in orthodontic patients was shown in a study by Sonesson *et al.* (38), consistent with the present study. Most of the studies evaluating the preventive effect of fluoride varnish have reported a lower incidence of white spot lesions than placebo varnish during orthodontic treatment (1, 36, 37). However, in a controversial study by Kirschneck *et al.*, no difference was observed between fluoride and placebo groups 4 and 20 weeks after the initiation of treatment (39). This discrepancy might be attributed to the type of fluoride product they used, i.e. amine fluoride, which has been reported to be less effective than sodium fluoride (40).

Some clinical trials evaluating the effect of different xylitol products, such as topical syrups (9), tablets (41), and wipes (7), have shown a decrease in caries incidence in comparison to the control groups in young children. In orthodontic patients, controversies exist among studies regarding the efficacy of xylitol products. Stecksén-Blicks and Isotupa (12, 22) showed that the *S. mutans* levels of plaque and saliva significantly reduced in children with orthodontic appliances that received chewing gum containing xylitol. Although no study was found on the effect of 10% xylitol varnish clinically, these findings are similar to those of the present study regarding the effectiveness of 10% xylitol varnish compared to placebo varnishes. However, a clinical study by Masoud *et al.* (13) showed that xylitol gum or tablet did not have a clinical or bacterial benefit in patients with fixed orthodontic appliances. In this study, topical fluoride was added to all the groups in addition to routine oral hygiene instructions, which might have played the role of a confounding factor. Furthermore, an ex vivo study by Ho *et al.* showed that a 10% xylitol medium exhibited no significant antibacterial effects (14). In this study, the extracted premolars with brackets were evaluated after exposure to xylitol media with different concentrations and

S. mutans in 24-hour biofilms. Although *S. mutans* counts were not determined in the present study, it should be noted that bacterial inhibition is only one of the anticariogenic mechanisms of xylitol (42). Furthermore, the clinical condition in which the present study was performed is different from the ex vivo one, and the xylitol varnish was applied on the clean teeth before any plaque formation.

In the present study, the effect of 20% xylitol was similar to the placebo at all follow-up intervals and followed the natural remineralization process of the oral cavity accomplished by routine plaque control procedures. In a recent study conducted by Silva *et al.* (23), the enamel mineralization was more with fluoride varnish compared to 20% xylitol and placebo varnish, consistent with the present study. Furthermore, in an in vitro study by Pereira *et al.*, salivary xylitol concentrations were evaluated after the application of 20% and 10% xylitol varnish (18). They reported that 10% xylitol exhibited a more sustained release of xylitol over a longer period. In the clinical condition of the present study, it seems that the period of high concentration of 20% xylitol in the saliva was too short to have any effect after three months, and it was similar to placebo varnish on all follow-up visits. However, in the 10% xylitol group, changes in mineral loss from the beginning of the treatment up to the sixth month were minimal, which might be attributed to the sustained release of xylitol from this concentration, consistent with a study by Pereira *et al.* (18).

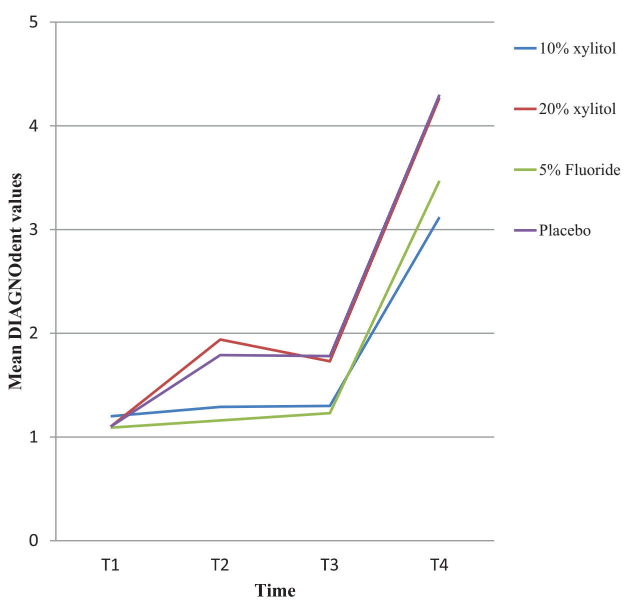

Figure 2. Comparison of mean DIAGNOdent values between the groups at four time intervals. T_1 (baseline), T_2 (three months after treatment began), T_3 (six months after treatment began), and T_4 (at the end of orthodontic treatment). The mean and *P*-value for each group are explicated in Table 2.

In this regard, some studies have addressed the effect of xylitol on enamel erosion, which represents surface demineralization (43, 44), and showed that high concentrations of xylitol solutions (20% and 40%) were unable to reduce surface mineral loss. This was explained by the pores on the enamel surface that prevent the penetration of high concentrations of xylitol (43).

Furthermore, some in vitro studies have evaluated the effect of 20% xylitol varnish and solution on the remineralization of artificial carious lesions (21, 31, 45), reporting that 20% xylitol was only effective in remineralizing deep layers but not the outermost surface of the enamel. These explanations can justify the ineffectiveness of 20% xylitol varnish in preventing white spot lesions in the present study.

Also, some evidence exists that in high-concentration fluoride varnishes, fluoride particles are separated from the resin and settle on the side of the storage bottle, resulting in a lack of fluoride uniformity (46). The lack of uniformity and a high fluoride release rate into the oral environment reduce the fluoride available for the enamel surface to absorb (46). This phenomenon might be generalized to other varnishes, like xylitol, and justify the low performance of high-concentration xylitol varnishes in preventing enamel demineralization.

Incorporation of xylitol into a varnish formulation provides sustained release of xylitol due to long-term adhesion to the enamel surface, without patient compliance for the consumption of the xylitol, which is an important advantage over the other xylitol products (16). The results of the present study revealed that both 10% xylitol and 5% fluoride are effective in caries control, and 10% xylitol varnish could be an alternative to 5% fluoride with almost good long-term effectiveness. These two varnishes are especially beneficial in the first several months of orthodontic treatment when the oral environment has changed and patients have not adopted convenient oral hygiene control. On the other hand, 20% xylitol varnish is ineffective in preventing white spot lesions. Considering the temporary discoloration of the teeth, which was reported by some patients in this group, it seems that the use of 20% xylitol varnish is not cost-effective.

More clinical studies are necessary for future investigations to discover the preventive effect of xylitol varnish in patients with poor oral hygiene. Furthermore, it is suggested that the remineralization effect of xylitol varnish be evaluated in patients exhibiting white spot lesions after debonding orthodontics appliances.

Limitations

1. This research was performed as a single-center trial.
2. The exact amount of toothpaste and the other fluoride supplements that the patients might have used during the trial were not completely controlled.

Table 3. Comparison of DIAGNOdent numbers of each group at different time intervals based on intention-to-treat (ITT) analysis (T_1: Before intervention, T4: at the end of treatment).

		No.	Mean (±SD)	95% CIs	*P*-value	*P*-values versus placebo group
T_1	10% Xylitol	30	1.29 (±0.76)	0.93–1.66	0.868	0.903
	20%Xylitol	30	1.10 (±0.88)	0.69–1.51		0.999
	5% Fluoride	30	1.07 (±0.88)	0.66–1.48		0.991
	Placebo	30	1.14 (±1.036)	0.65–1.62		
	Total	120	1.15 (±0.88)	0.95–1.35		
T_4	10% Xylitol	30	3.31 (±1.27)	2.70–3.93	0.092	0.104
	20% Xylitol	30	4.27 (±1.62)	3.51–5.03		1.000
	5% Fluoride	30	3.56 (±1.46)	2.88–4.25		0.275
	Placebo	30	4.30 (±1.55)	3.58–5.03		
	Total	120	3.87 (±1.52)	3.53–4.21		

Table 4. Distribution of white spot lesions based on Gorlick index after removing the fixed orthodontic appliances.

	No.	Gorlick index, no. (%)				*P-value*	Odds ratio (95% CI)
		0	1	2	3		
Per-protocol analysis							
10% Xylitol	270	226 (83.7%)	41 (15.2%)	3 (1.1%)	0 (0.0%)	0.000*	0.43 (0.28–0.64)
20% Xylitol	300	190 (63.3%)	99 (33.0%)	8 (2.7%)	3 (1.0%)	0.174	1.26 (0.90–1.78)
5% Fluoride	290	222 (76.6%)	67 (23.1%)	1 (.3%)	0 (0.0%)	.033*	0.67 (0.46–0.96)
Placebo	290	199 (68.6%)	76 (26.2%)	13 (4.5%)	2 (0.7%)		
Total	1150	837 (72.8%)	283 (24.6%)	25 (2.2%)	5 (0.4%)		
Intention-to-treat analysis							
10% Xylitol	300	240 (80.0%)	56 (18.7%)	4 (1.3%)	0 (.0%)	0.002*	0.55 (0.38–0.80)
20% Xylitol	300	190 (63.3%)	99 (33.0%)	8 (2.7%)	3 (1.0%)	0.143	1.28 (0.91–1.80)
5% Fluoride	300	230 (76.7%)	69 (23.0%)	1 (.3%)	0 (.0%)	0.035*	0.67 (0.47–0.97)
Placebo	300	207 (69.0%)	78 (26.%)	13 (4.3%)	2 (.7%)		
Total	1200	867 (72.2%)	302 (25.2%)	26 (2.2%)	5(0.4%)		

**P-value < 0.05*. The presence of any WSL (Score 1 + 2 + 3) in treatment groups was compared to the placebo group using binary logistic regression.

Generalizability

Caution should be exercised in interpreting the results of this study because this study was a single-center study on patients with adequate oral hygiene. The generalizability of the results might be limited to the patients with the characteristics mentioned above.

Conclusion

Based on the results of the current study, it was concluded that 10% xylitol, similar to fluoride varnish, is a useful supplement to control enamel demineralization and white spot lesion formation during orthodontic treatment. Even application of this varnish twice with an interval of three months at the beginning of orthodontic treatment could have a long-term effect on preventing enamel demineralization and white spot lesion formation with slightly better performance than the fluoride varnish. On the other hand, 20% xylitol seems to have no advantages over routine oral hygiene control in orthodontic patients.

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Conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Data availability

The data that support the finding of this study are available on request from corresponding author.

Registration and protocol

The trial was registered under the code IRCT20180913041032N1 at the Iranian registry of clinical trials, and its protocol is available at www.IRCT.ir.

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