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ORIGINAL ARTICLE

Efficacy of fluoride varnish for preventing white spot lesions and gingivitis during orthodontic treatment with fixed appliances—a prospective randomized controlled trial

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Abstract
Objectives The development of white spot lesions around orthodontic brackets and gingivitis is a common problem during orthodontic treatment with fixed appliances. This prospective randomized double-blind controlled clinical trial investigated the preventive efficacy of a one-time application of two commonly used fluoride varnishes in patients with low to moderate caries risk.
Materials and methods Ninety adolescent orthodontic patients with a low to moderate caries risk were prospectively randomized to three groups of 30 patients each: (1) standardized dental hygiene with fluoride toothpaste and one-time application of placebo varnish (control) or (2) of elmex® fluid or (3) of Fluor Protector S on all dental surfaces at the start of fixed therapy. The extent of enamel demineralization and gingivitis was determined with the ICDAS and the gingivitis index (GI) at baseline and after 4, 12, and 20 weeks.
Results Each treatment group showed a significant increase of the ICDAS index, but not of the GI over the course of time with no significant intergroup differences detectable.
Conclusions A one-time application of fluoride varnish at the start of orthodontic treatment did not provide any additional preventive advantage over sufficient dental hygiene with fluoride toothpaste with regard to formation of white spots and gingivitis in patients with a low to moderate caries risk.
Clinical relevance In dental practice, patients often receive an application of fluoride varnish at the start of orthodontic treatment with fixed appliances. However, the efficacy of this procedure is still unclear.

Keywords Fluorides, Topical, White Spots, Gingivitis, Orthodontics.

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Introduction

White spot lesions (WSL) as a sign of initial enamel demineralization and subsequent caries [1] are common undesired side effects during orthodontic treatment with fixed appliances [2]. Reasons for the high incidence of WSL are the treatment-associated restrictions in effective dental hygiene [3] and the increased retention of pathogenic biofilms (dental plaque) due to the presence of brackets and synthetic bonding materials [4]. Pathogenic biofilms may cause enamel demineralization as well as inflammation of the gingiva [5]. Because WSL fail to recede completely in most patients, preventing such lesions should be the primary objective of orthodontic practitioners and dentists [6].

The incidence and prevalence of enamel demineralization and plaque-induced gingivitis are closely related with the willingness of patients to use sufficient preventive measures [5, 7]. It is the responsibility of orthodontists to prevent enamel demineralization and plaque-induced gingivitis by choosing a suitable prophylactic system. Preventive measures need to be coordinated in close cooperation between orthodontists and referring dentists, who often support the prophylactic management of patients, albeit to different degrees [8].

Fluoride has been proven to prevent enamel demineralization and caries; therefore, various products containing fluoride have been developed to reduce the risk of WSL development

for both dentists and patients during orthodontic treatment with fixed appliances. Several studies have shown the effectiveness of domestic dental care products containing fluoride, such as toothpaste, mouth rinses, and gels. These products have also been proven to be effective in preventing gingivitis [9–11]. However, because the effectiveness of such products largely depends on the cooperation of the patients [9], orthodontists often additionally apply a varnish with a high content of fluoride at the start of therapy. Several studies have shown the protective effect of fluoride varnishes [12, 13]. Regular application is recommended, particularly in patients with a high risk of developing caries and with limited access to fluoride products [14, 15].

In dental practice, fluoride varnish is often applied at the start of orthodontic therapy with fixed appliances. However, despite the proven preventive effect of fluorides [16] and fluoride varnishes [13], it is not yet known whether this one-time application of fluoride varnish at the beginning of fixed orthodontic treatment has an additional protective effect compared to sufficient domestic dental hygiene with fluoride toothpaste (1500 ppm F^-) in patients with a low to moderate caries risk. This question was investigated in the present prospective randomized placebo-controlled clinical study by using the common fluoride products elmex® fluid (10,000 ppm F^-) and Fluor Protector S (7700 ppm) over a period of 20 weeks.

Materials and methods

This single-center prospective randomized double-blind placebo-controlled clinical trial was conducted in Germany between November 2013 and June 2014 and included 90 orthodontic patients, who were randomly assigned to three groups of 30 patients each (1:1:1; three parallel treatment arms), receiving either a one-time application of placebo varnish, elmex® fluid varnish or Fluor Protector S varnish at the beginning of fixed orthodontic treatment. This corresponds to current clinical recommendations (ADA) for patients with low to moderate caries risk, suggesting a one-time fluoride application every 6 months.

An independent investigator, not otherwise associated with the study, prepared 90 envelopes that contained a code of one of three different colors (yellow, blue, and red). This color code allowed the allocation of each patient to one of the three treatment arms (30 envelopes per arm). Each envelope was labeled with a 4-digit number generated by an electronic random number generator (computer).

All adolescent patients aged 10–17 years scheduled to receive fixed orthodontic treatment (buccal technique) were informed by the same orthodontist about the study project. On participation, meeting the eligibility criteria and giving informed consent, the patients were randomly allocated by the instructing orthodontist to one of the three treatment arms by successively opening the envelopes (one per patient) starting with the smallest number available.

Exclusion criteria were low compliance and motivatability to conduct sufficient dental hygiene after proper instruction and reevaluation as defined by failure to adhere to weekly prophylactic office visits before treatment (missing more than one) or a Silness/Löe plaque index (1964) of ≥1.0 at the start of orthodontic treatment (baseline); dental surfaces with an ICDAS index of ≥2 at baseline; the presence of fillings and restorations, oral, systemic, metabolic, or mental disease; existing medication, alcohol abuse, nicotine, or drug consumption; periodontitis or periodontal disease; syndromes; cleft lip, jaw, and palate; and a supposed high risk of caries. The latter was assessed primarily by anamnesis and clinical examination [17]. If an anamnestic-clinical indication for high caries risk was found, an additional CRT bacteria test was performed (CRT® bacteria, Ivoclar Vivadent GmbH, Schaan, Liechtenstein) [18] with Mutans Streptococci or Lactobacilli counts exceeding 10^5 CFU/ml saliva set as exclusion criterion.

At the start of the study (T0) as well as after 4 (T1), 12 (T2), and 20 (T3) weeks, the extent of enamel demineralization (primary outcome) and gingivitis (secondary outcome) was determined according to the current guidelines of the International Caries Detection and Assessment System (ICDAS index) [19] and the Gingivitis Index (GI) [5] by the same blinded investigator. No changes to trial outcomes were made after the beginning of the study.

Before the start of therapy, each patient underwent professional tooth cleaning with fluoride-free polishing paste and received detailed instructions on dental hygiene according to a standardized prophylactic concept. This concept consisted of manual tooth cleaning with fluoride toothpaste (1500 ppm F^-)

Fig 1 Tested fluoride products in their original packaging. **a** elmex® fluid (GABA GmbH, 10,000 ppm F^-; 1 % amine fluoride, 0.925 % from Olaflur and 0.075 % from Dectaflur); **b** Fluor Protector S (Ivoclar Vivadent GmbH, 7700/29,000(dried) ppm F^-; 1.5 % ammonium fluoride). For patients with a low to moderate caries risk, current clinical recommendations (ADA) suggest a single application every 6 months, which does correspond to the setting of this study

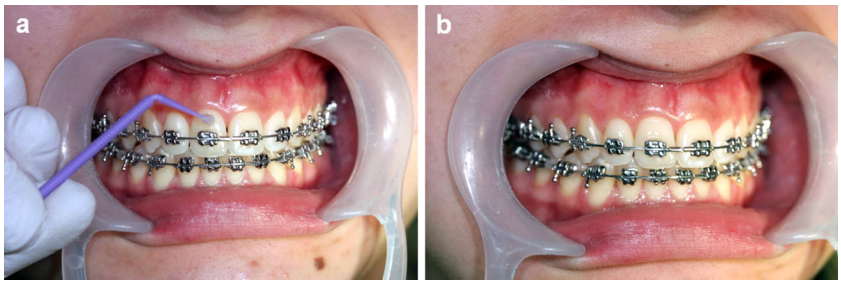

Fig 2 **a** Application of elmex® fluid (GABA GmbH) and Fluor Protector S (Ivoclar Vivadent GmbH) with a microbrush (applicator tip); **b** Condition after fluoride application and air drying

for 8 min twice a day and cleaning of the interdental spaces with dental floss or an interdental brush. Orthodontic treatment with fixed appliances was only started after a patient was able to perform an adequate dental prophylaxis at home, which was checked in regular weekly office visits with the patient demonstrating the brushing technique and usage of interdental floss/brush as well as by plaque evaluation with the Silness/Löe plaque index (1964). The execution of the cleaning procedures was re-evaluated and re-instructed at every office visit. All patients were instructed to also refrain from using additional fluoride-containing products. The level of fluoride of the regional drinking water was <0.2 ppm F^-.

After the patients had been fitted with fixed multi-bracket appliances (Silverstar 0.022“ Slot Roth Brackets, TeleDenta GmbH, Chemnitz, Germany; Transbond XT, 3 M Unitek, Monrovia, CA, USA), the tooth surfaces were cleaned and the oral cavity dried. A thin layer of 0.2–0.3 ml of elmex® fluid (Fig. 1a; GABA GmbH, Lörrach, Germany), Fluor Protector S (Fig. 1b; Ivoclar Vivadent GmbH, Schaan, Liechtenstein), or placebo vanish without any fluoride (70 % *w*/*v* ethanol, control group) was applied with a microbrush to all maxillary and mandibular dental surfaces with orthodontic brackets (Fig. 2a). After air-drying for 1 min (Fig. 2b), patients were asked to spit out and refrain from eating, drinking, and rinsing their mouth for 2 h. The study was conducted in a double-blinded manner, so that neither the investigators nor the patients knew which product was applied. At the beginning of the study, an independent investigator masked the products by randomly filling each of the three varnishes into identical color-coded plastic standard containers. All products were applied in the same way. The color code of the respective study group was only assigned to the applied product after the statistical analysis.

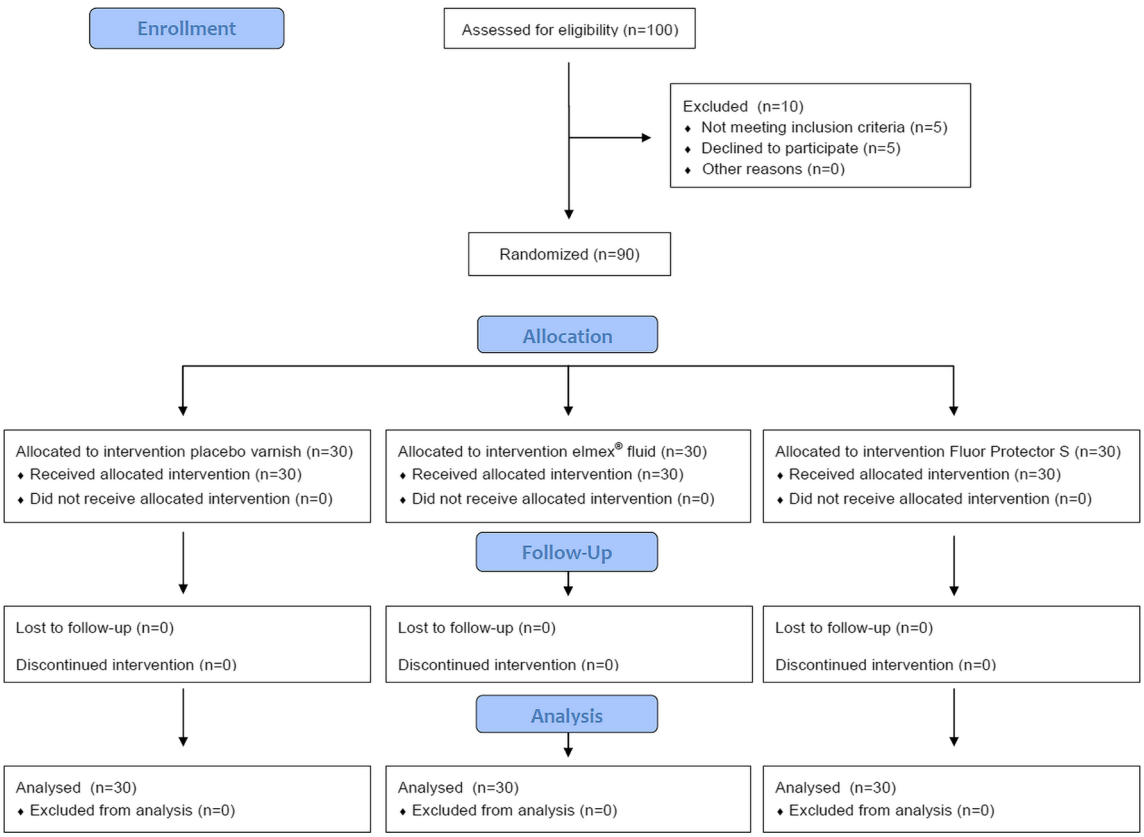

Fig 3 Patient flow during the trial

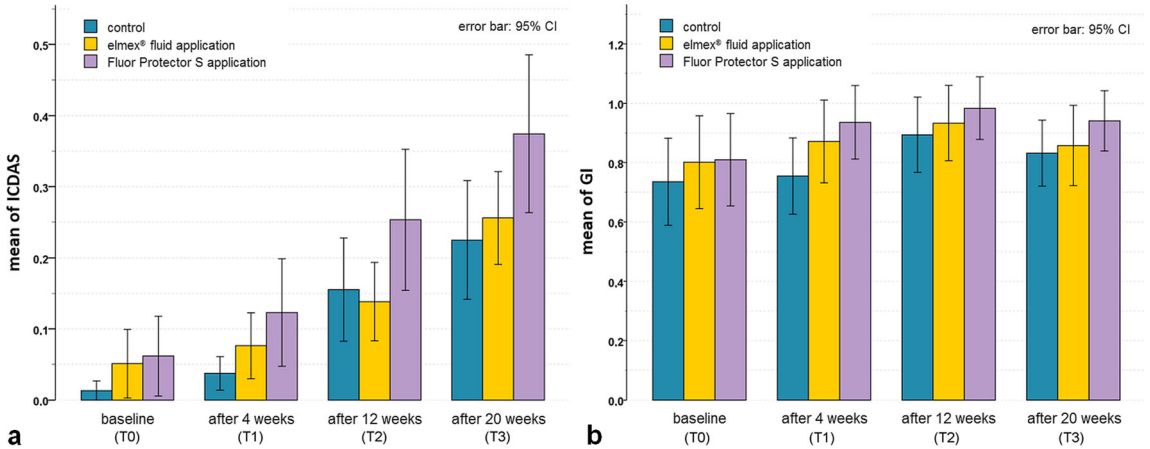

Fig 4 Mean ICDAS index (a) and GI (gingivitis index) (b) of the individual study groups and time points of examination with the corresponding 95 % confidence intervals, based on the mean ICDAS and GI values of each patient. *CI* confidence interval

The study design remained unchanged throughout the entire duration of the study. Statistical analysis was performed with the program IBM SPSS Statistics® 22 (IBM, Armonk, NY, USA). Before statistical analysis, the patient's arithmetic mean of the ICDAS and GI values of the individual tooth surfaces with an orthodontic bracket was calculated. The mean ICDAS and GI value for each patient was then used in statistical analysis. The required number of patients for sufficient intergroup statistical power of ≥80 % for the primary outcome ICDAS index after 4 weeks was defined on the basis of unpublished pre-data of single patients in consideration of a dropout rate of 10 % by means of an a priori power analysis with the program G*Power 3.1.9 [20]. No interim data analyses were performed. Because of deviations of the data from normal distribution (Shapiro-Wilk test and visual histogram analysis) and homoscedasticity (Levene test and ZPRED vs. ZRESID scatterplots), significance testing between the study groups was done with non-parametric two-sided independent H tests according to Kruskal–Wallis. The homogeneous distribution of groups for the categorical variable gender was investigated by means of Fisher's exact test. Significance tests with regard to changes in the ICDAS and the GI indices over the course of time (T0 to T3) were done with non-parametric dependent ANOVA tests according to Friedman. The level of significance was set at $p \leq 0.05$, and all p values referring to an identical outcome parameter (ICDAS or GI index) were adjusted according to the Bonferroni-Holm method for multiple testing (avoiding an increase in alpha error). To determine the clinical relevance of the results, we calculated effect sizes according to the Pearson correlation coefficient r and Cramér's V: r or V ≥ 0.5, 0.3, and 0.1 corresponds to a large, medium, and small effect or difference [21].

Results

During the recruitment period between November 2013 and June 2014, 100 patients were screened for possible inclusion in total (Fig. 3). After thorough examinations and interviews, three patients were ineligible because of taking medication for mental disease and two patients because of nicotine consumption (one of those with mental disease). One patient had manifest caries and five patients did not want to participate in the study. Enrollment was stopped, when 90 participants, predetermined by statistical power analysis, were randomly recruited, 30 for each treatment arm. The ratio of male to female patients was 14:16 for the placebo group, 14:16 for the elmex® fluid group, and 16:14 for the Fluor Protector S group. All 90 included patients received the intended treatment and were analyzed for the primary and secondary outcome. For all participants, no exclusion criterion applied over the course of the study; thus, no dropouts occurred. No harms or unintended side effects could be observed in any of the treatment groups.

The three study groups did not show any significant difference in the mean ICDAS or GI index at any of the four time points (T0 to T3) (Fig. 4, Table 1). However, the mean ICDAS index had significantly increased in all three study groups over the course of the investigation (T0 to T3) (Fig. 4a, Table 2). The GI index had not significantly changed in any of the three study groups (Fig. 4b, Table 2). When evaluating frequency

Table 1 Kruskal–Wallis H tests for investigating any significant differences in the ICDAS and GI index at the different time points (T0 to T3)

Time point	Parameter	H (df)	*p*	*r*
Baseline status (T0)	ICDAS index	1.729 (2)	0.421	0.09
	GI index	1.119 (2)	1.000	0.00
After 4 weeks (T1)	ICDAS index	2.812 (2)	0.750	0.03
	GI index	4.480 (2)	0.400	0.09
After 12 weeks (T2)	ICDAS index	2.746 (2)	0.500	0.07
	GI index	0.771 (2)	0.680	0.04
After 20 weeks (T3)	ICDAS index	6.048 (2)	0.200	0.13
	GI index	1.933 (2)	1.000	0.00

Table 2 ANOVA tests according to Friedman to investigate any significant differences in the ICDAS index and gingivitis index (GI) over the period of investigation (T0 to T3)

Test group	Parameter	X^2_F (df)	p	r
Control group	ICDAS index	66.327 (3)	<0.001***	>0.59
	GI index	9.836 (3)	0.060	0.40
elmex®-fluid group	ICDAS index	75.704 (3)	<0.001***	>0.59
	GI index	3.469 (3)	0.650	0.08
Fluor Protector S group	ICDAS index	75.220 (3)	<0.001***	>0.59
	GI index	2.684 (3)	0.443	0.14

***p<0.05

distributions of the individual tooth-specific ICDAS and GI values recorded (Fig. 5), these observations were confirmed with higher ICDAS values occurring more frequently from T0 to T3 and no distinct intergroup differences. No notable changes were found in frequency distribution for the GI values.

Kruskal–Wallis H tests showed that the study patients had been homogeneously allocated to the three study groups with regard to their age at the start of therapy (Fig. 6a; H = 0.434; df = 2; p = 0.805; r = 0.03) as well as with regard to the number of dental surfaces included in the index calculation (Fig. 6b; H = 5.012; df = 2; p = 0.082; r = 0.18). Homogeneous distribution had also been achieved regarding the allocation of male and female patients to the three study groups (Fisher's exact test): φ = 1.084; p = 0.627; V = 0.109.

Discussion

Twenty weeks after the start of therapy, the incidence of white spot lesions (WSL) and initial caries was significantly increased in the control group (only sufficient dental hygiene with fluoride toothpaste, placebo varnish) as well as in the groups of patients treated with one of the fluoride varnishes. This increase, represented by the elevation in the ICDAS index, showed that WSL located in the periphery of the brackets of a fixed appliance are a rapidly developing problem in orthodontic treatment. This finding corresponds with the results found in the previous studies [1, 22, 23]. Luccese and Gherlone [24], for instance, could show that the first 6 months are of particular importance in the development of WSL, because the frequently adolescent patients have to adapt their

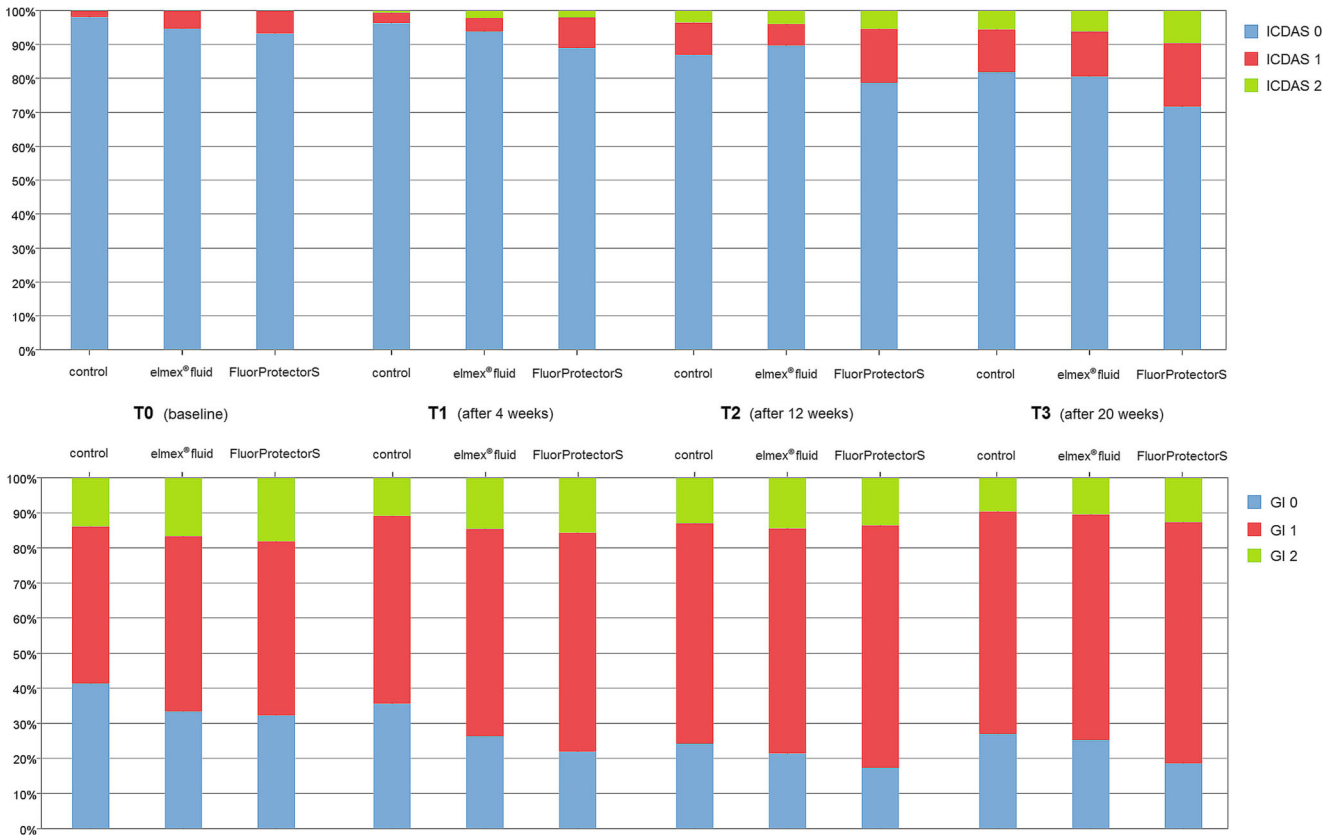

Fig 5 Frequency distribution of all tooth-specific ICDAS and GI value recorded, shown for the individual study groups and time points of examination

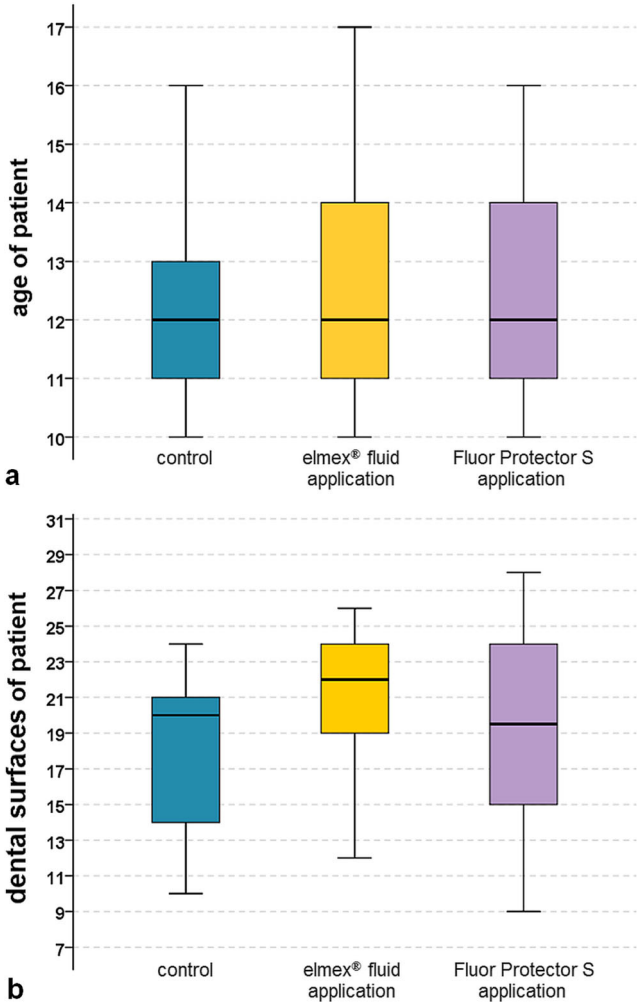

Fig 6 Patient age (**a**) and number of dental surfaces (teeth) with an orthodontic bracket per patient (**b**) for each of the three study groups. Mean values (crossbar), interquartile range (IQR box), and minimum and maximum values (whiskers)

hygienic practices to the requirements of orthodontic treatment. The results also showed that WSL cannot be prevented in all patients, even in the case of appropriate dental hygiene with fluoride toothpaste and use of additional preventive measures, such as the application of fluoride varnish [25]. The most probable reason is the presence of plaque predilection sites caused by the fixed appliance that impede effective cleaning and plaque removal by means of domestic dental care [3].

Twenty weeks after the fitting of a fixed multi-bracket appliance, neither of the two fluoride varnishes elmex® fluid and Fluor Protector S had significantly reduced the incidence of WSL and initial caries in the respective study group in comparison to the control group with only standardized domestic dental care and placebo varnish. This finding indicates that the application of topical fluoride with fluoride toothpaste as part of sufficient daily dental hygiene already has an adequate protective effect in patients with a low to moderate caries risk. Therefore, the caries-protective effects of fluoride toothpaste, which locally inhibit demineralization and increase remineralization processes [26], could not be further increased by the one-time application of additional fluoride at the beginning of fixed orthodontic treatment. In contrast, several in vitro and in vivo studies have shown the caries-protective effect of elmex® fluid, Fluor Protector S, and other fluoride varnishes in orthodontic treatment [12, 13, 27–30]. In vitro, this finding is probably caused by insufficient simulation of the remineralizing effects of saliva [31]. In vivo, this result may have been caused by the choice of study patients (for instance, patients with a different caries risk), the study design (retrospective, lack of placebo control, randomization, or blinding), and lack of standardized domestic dental hygiene (for example, insufficient dental hygiene of the study participants). After the topical application of elmex® fluid, Dénes et al. [13] observed a significantly lower incidence of WSL in patients undergoing orthodontic treatment with fixed appliances and standardized domestic dental hygiene. However, this finding was most likely caused by the use of fluoride-free toothpaste, which contrasted with the present study.

None of the three study groups showed any significant change in the GI between T0 and T3. This result indicates that sufficient dental hygiene may keep the gingiva free from inflammation during orthodontic treatment with fixed appliances. This finding is also in accordance with the model illustrating the development of plaque-induced gingivitis established by Löe et al. [5]. The discrepancy to the observed increase in the ICDAS index is probably due to the fact that the standardized domestic dental care may completely remove the plaque from smooth dental surfaces and the marginal periodontium, but not from the immediate periphery of orthodontic appliances such as brackets or arches.

The present prospective, randomized, placebo-controlled, and double-blind study was conducted to achieve results with a high level of evidence that could be applied to the overall population. Standardization of both dental hygiene [9, 13] according to a strict prophylactic concept ensured the valid comparability of the study groups. The distribution of the three study groups did not significantly differ with regard to the factors gender, age, and the number of dental surfaces with an orthodontic bracket attached; thus, the randomization process ensured the homogeneity of the study groups with regard to factors that may potentially influence both the ICDAS index as well as the GI index. Potentially harmful influences of the intervention, such as overdoses of fluoride, could be avoided by the targeted application of the fluoride products by the treating orthodontist.

One limitation of this study is the lack of supervision of domestic dental care, which was not possible for ethical and logistic reasons. Thus, deviations from the standardized domestic prophylactic concept may have been possible in single

cases. Because of the randomization of the patients, however, no significant distortion of the results is to be expected. A further limitation is the lack of additional control groups, who are only treated with one of the two fluoride varnishes, but who do not follow any domestic prophylactic concept. However, the establishment of such study groups was not possible for ethical reasons. Therefore, it was not possible to evaluate, whether the prophylactic one-time application of the investigated fluoride varnishes - which did not show any additional protective effects in patients with sufficient dental hygiene with fluoride toothpaste - may have protective effects in patients with poor dental hygiene, as indicated by several in vitro studies [12, 27, 30]. Furthermore, the present study only included patients with a low to moderate caries risk. Thus, we were unable to evaluate possible protective effects of the fluoride varnishes in patients with a high caries risk or insufficient dental hygiene.

Conclusions

- The one-time application of the fluoride varnishes elmex® fluid or Fluor Protector S at the start of orthodontic treatment with a fixed multi-bracket appliance did not yield any additional preventive advantage over sufficient domestic dental hygiene with fluoride toothpaste in patients with a low to moderate caries risk.
- Therefore, the application of the investigated varnishes does not guarantee absolute protection against the development of white spot lesions.
- A progression of gingival inflammation is not to be expected within the first 5 months after the start of therapy in patients with sufficient dental hygiene.
- Patients and legal guardians must be fully informed about the importance of sufficient domestic preventive measures as well as about the risk of enamel demineralization during orthodontic treatment with fixed appliances.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals.

Conflict of interest The authors report no financial or other conflict of interest relevant to this article, which is the intellectual property of the authors. Furthermore, no part of this article has been published before or is considered for publication elsewhere. It has been approved by all authors and the affiliated institution.

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Informed consent Informed consent was obtained from all individual participants included in the study and in addition - if under age - from their legal guardians.

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