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ORIGINAL ARTICLE

Remineralization effect of NaF, NaF with TCP, NaF with CPP-ACP and NaF with CXP varnishes on newly erupted first permanent molars: A randomized controlled trial

Merve Erkmen Almaz[1] | Nur Burcu Ulusoy[2] | Aylin Akbay Oba[2] | Aysun Dokumacı[2]

[1]Kırıkkale University, Kırıkkale, Turkey

[2]Private practice, Ankara, Turkey

Correspondence
Merve Erkmen Almaz, Kırıkkale University, Kırıkkale, Turkey.
Email: dt.merveerkmen@gmail.com

Abstract

Introduction: The aim of this study was to evaluate the remineralization effect of NaF, NaF with TCP, NaF with CPP-ACP and NaF with CXP varnishes on newly erupted first permanent molars using laser fluorescence (LF) method. The study was a randomized, double-blind, controlled trial with four parallel groups.

Methods: The study was carried out in 48 high caries-risk children (DMFS >8), aged 6–7 years with newly erupted permanent first molars (initial lesion with 13 < LF value<30). A total of 140 teeth were divided randomly into four groups ($n = 35$): **G1.**Duraphat Varnish containing 5% NaF, **G2.** Clinpro™ White Varnish containing 5% NaF with TCP, **G3.**Embrace™ Varnish containing 5% NaF with CXP, **G4.** MI Varnish containing 5% NaF with CPP-ACP. All dental treatments of the patients were completed before the varnish application. The varnishes were applied to the targeted teeth at baseline, 1 and 3 months. Patients were called for follow-up appointments at 1, 3 and 6 months, and LF scanning was used to monitor mineralization changes. Data were analysed statistically by Wilcoxon signed-rank and Mann–Whitney *U*-tests.

Results: In total, 40 children (122 teeth) completed the trial. At the end of 6 months, the amount of reduction in LF values (indicating remineralization) are as follows: NaF with CXP(6.87 ± 4.32) < NaF with TCP(7.36 ± 7.05) < NaF(7.40 ± 7.03) < NaF with CPP-ACP(8.33 ± 4.90). All of the varnishes resulted in significant decrease in LF measurements and there was no significant difference between control (NaF alone) group and other groups. Only MI varnish had a significantly greater remineralization effect than Embrace™ Varnish ($p < 0.05$).

Conclusion: As a non-invasive approach, CPP-ACP, TCP and CXP containing NaF varnishes have the potential to remineralize initial caries lesions on permanent first molars in high caries-risk children.

KEYWORDS
antimicrobial agents, antiplaque agents, conservative, fluoride varnishes

1 | INTRODUCTION

Dental caries are defined as multifactorial, chronic, infectious diseases and are characterized by the localized destruction of hard tissues from organic acids as a result of the interaction of cariogenic bacteria with fermentable dietary carbohydrates.[1] The formation of caries begins with the creation of organic acids as a result of bacterial fermentation and environmental pH levels falling below the critical pH level of 5.5.[2] The decrease in plaque pH levels below 5.5 causes the start of the demineralization period.[3] Demineralization is the transfer of H^+ ions from plaque into carious lesions, and the dissolution of mineral ions from the tooth surface towards the plaque.[4] Remineralization is defined as the process which promotes ion deposition into demineralized enamel to ensure structural integrity and produce mineral gain.[5] In the remineralization of enamel, saliva, the biofilm layer, Ca, PO_4 and F-concentrations of remineralizing agents and the solubility of these minerals plays an important role.[6]

In the treatment of initial carious lesions, the main objective is that remineralization becomes more effective than demineralization by using remineralizing agents.[7] Fluorides have been used for many years for the prevention and remineralization of initial carious lesions.[8] In recent years, with adding new substances to fluoride varnishes it was aimed to gain the advantage of increasing their anticaries and remineralization potential. In the present study, Clinpro™ White Varnish, a topical varnish containing 5% sodium fluoride (NaF) with tri-calcium phosphate (TCP), was used. Clinical studies that focus on and employ this varnish are few. Clinpro™ White Varnish, however, was reported to be effective for caries prevention in preschool children[9] and in treating initial primary enamel lesions,[10] and it also has high remineralization efficacy.[11] Another varnish that was used in the present study, Embrace™ Varnish, contains 5% NaF with xylitol-coated calcium and phosphate (CXP). According to the manufacturer, the xylitol coating prevents calcium and phosphate salts from reacting until they encounter saliva. The saliva dissolves the xylitol and releases the calcium and phosphate ions, forming protective fluorapatite when reacting with the fluoride ions in saliva.[12] There is no clinical study evaluating the remineralization effect of Embrace Varnish. MI Varnish, which was recently introduced to the market, contains 5% NaF with casein phosphopeptide amorphous calcium phosphate (CPP-ACP). MI Varnish reportedly has a high release of calcium and fluoride ions.[13] Moreover, previous studies report that CPP-ACP was a promising agent with a significant remineralizing effect.[14,15] In the present study, we used Duraphat (Colgate) Varnish as a control group, which contains only 5% NaF. Duraphat is reportedly effective in remineralization,[16] reduces the number of carious lesions on permanent teeth in children who are at high risk of caries,[17] and increases the fluoride content of enamel in deciduous teeth.[18]

A literature search found that no studies have been conducted on the in vivo remineralization effect of these varnishes on newly erupted first permanent molars. The aim of this study was to evaluate and compare the efficacy of NaF, NaF with TCP, NaF with CPP-ACP and NaF with CXP varnishes on newly erupted first permanent molar teeth. The following null hypothesis was tested: Different substances added to NaF varnishes provide a greater remineralization effect than NaF alone.

2 | MATERIALS AND METHODS

2.1 | Ethics

The study was carried out with Kırıkkale University Ethical Committee approval (24.01.2017, 03/03). The study protocol was explained to the parents/guardians of the children, and all participants' parents/guardians signed informed consent forms. The study protocol (NCT04124887) was approved by the institutional review board.

2.2 | Study group

To determine the sufficient size of the study group, G*Power software, version 3.0.10 (Kiel, Germany © 1992–2008) was used. A total sample size of 112 teeth (28 per subgroup) was required (significance level of 5% with 90% power). Considering the loss of patients during the follow-up period, it was decided to include 35 teeth per subgroup (a total of 140 teeth).

The study was carried out in 48 healthy, high caries risk children (DMFS >8) aged 6–7 years, with newly erupted permanent first molars, who were referred to the Paediatric Dentistry Clinic of Kırıkkale University, Faculty of Dentistry, Kırıkkale, Turkey. Teeth were selected with the following inclusion criteria: (1) teeth with laser fluorescence (LF) values greater than 13 and less than 30, (2) no visible cavitation on the tooth surface and (3) fully erupted permanent first molar teeth.

2.3 | Study design

The study was a randomized, double-blind, controlled study with four parallel groups.

2.4 | Randomization

Simple randomization was performed by an assistant who was not involved in the study. The children were unaware of their allocation to the study groups. The children were asked to choose numbered papers from 'one to four'. On the papers there were numbers 1/2/3 or 4 (indicating group numbers; Group 1: Duraphat Varnish, Group 2: Clinpro™ White Varnish, Group 3: Embrace™ Varnish, Group 4: MI Varnish.) After the number of teeth in a group reached 35, paper with the number of that group was excluded. The children were asked to choose one of the remaining numbers. The restriction of simple randomization was eliminated in this way by the assistant.

A total of 140 teeth (48 patients) were divided randomly into four groups, and the varnishes were applied to the targeted teeth at baseline, one and 3 months. In a patient's mouth, if there was more than one first molar to be included in the study, one varnish was used for the targeted teeth. The groups were comprised as follows:

Group 1: Duraphat Varnish containing 5% NaF (Colgate-Palmolive, $n=35$ teeth, 12 children).

Group 2: Clinpro™ White Varnish containing 5% NaF with TCP (3 M ESPE, $n=35$ teeth, 12 children).

Group 3: Embrace™ Varnish containing 5% NaF with CXP (Pulpdent, $n=35$ teeth, 12 children).

Group 4: MI Varnish containing 5% NaF with CPP-ACP (GC, $n=35$ teeth, 12 children).

All dental treatments were completed before varnish application, and oral hygiene instructions were given to all children at the start of the study. Patients were called for follow-up appointments at 1, 3 and 6 months, and in the follow-up period, for the primary outcome, the DIAGNOdent device (LF scanning) was used to monitor mineralization changes. If a patient was excluded because of loss to follow-up; that patient's teeth, included in the study, are removed from the group they are in.

All the procedures, about blinding for the authors and patients (random allocation sequence with numbered papers, enrolling participants, calling the patients follow-up appointments, number of patient and teeth loss to follow-up), were carried out by the assistant who was not involved in the study.

2.5 | Laser fluorescence measurements

Laser Fluorescence (LF) measurements were performed using DIAGNOdent pen 2190 (KaVo) according to the manufacturer's instructions. The whole fissure was scanned with the DIAGNOdent pen fissure probe that was moved along the fissure, and the highest (peak) value was recorded. Measurements were made at baseline, after 1 month, 3 months and 6 months. All measurements were made before the varnish application. Before every measurement, the device was calibrated according to the manufacturer's instructions and all teeth were isolated with cotton rolls and dried before using the DIAGNOdent pen 2190. All the measurements were carried out by a trained paediatric dentistry postgraduate student (N.B.U) under the supervision of an author (M.E.A) who had clinical experience using the DIAGNOdent pen 2190 in previous clinical studies. The authors N.B.U. and M.E.A. were calibrated by evaluating 50 teeth not included in this trial. After calibration, kappa statistic was used to test interexaminer reliability and kappa score was found to be 0.89.

With the help of the assistant, who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions, the authors and the patients were blinded to the groups during LF measurements.

Two measurements were made per tooth. The data from the two measurements were combined and the average for the LFpen measurement was obtained for each tooth.

For the analysis, LF measurements were scored to indicate the different stages of the carious lesions on newly erupted permanent first molars (Table 1).

2.6 | Statistical analysis

LF measurements were compared with the baseline, 1 month, 3 months and 6 months after treatment within and between groups.

The data were analysed using SPSS (SPSS Inc., ver. 15). The Shapiro-Wilks test was used for normality testing. Because the data were not normally distributed, non-parametric tests were used for comparison. Moreover, the differences between the follow-up periods for each group were analysed by the Wilcoxon signed-rank test, and the Mann–Whitney *U*-test was used for comparison between groups. A *p*-value of less than 0.05 was considered statistically significant.

3 | RESULTS

A total of 168 teeth of 58 children, were assessed for eligibility and 140 teeth of 48 children met eligibility criteria and were randomized between February 2017 and February 2018. Eight (five teeth of two patients from group 1, five teeth of three patients from group 2, three teeth of one patient from group 3 and five teeth of two patients from group 4) out of 48 children were excluded from the study because they did not attend regular follow-up appointments (Figure 1). The remaining 40 children (23 female, 17 male) completed trial and a total of 122 (66 upper teeth, 56 lower) first permanent molar teeth were evaluated. The mean LF values in all groups at baseline and follow-up appointments are shown in Table 2.

3.1 | Comparison within groups

Table 3 shows the comparison of laser fluorescence measurements within and between groups according to different time intervals.

In the NaF Varnish group, LF values decreased significantly at 3rd month and 6th month follow-up intervals according to baseline, indicating significant remineralization ($p<0.001$). Although there was no significant difference in baseline vs. 1st month and 3rd month vs. 6th month values, mean LF values were decreased ($p=0.281$ and $p=0.097$, respectively).

TABLE 1 Ranges for DIAGNOdent Pen measurements (manufacturer recommendation).

Score	Diagnodent value	Criteria
0	0–13	Healthy tooth substance
1	14–20	Beginning demineralization
2	21–29	Strong demineralization
3	>30	Dentine caries

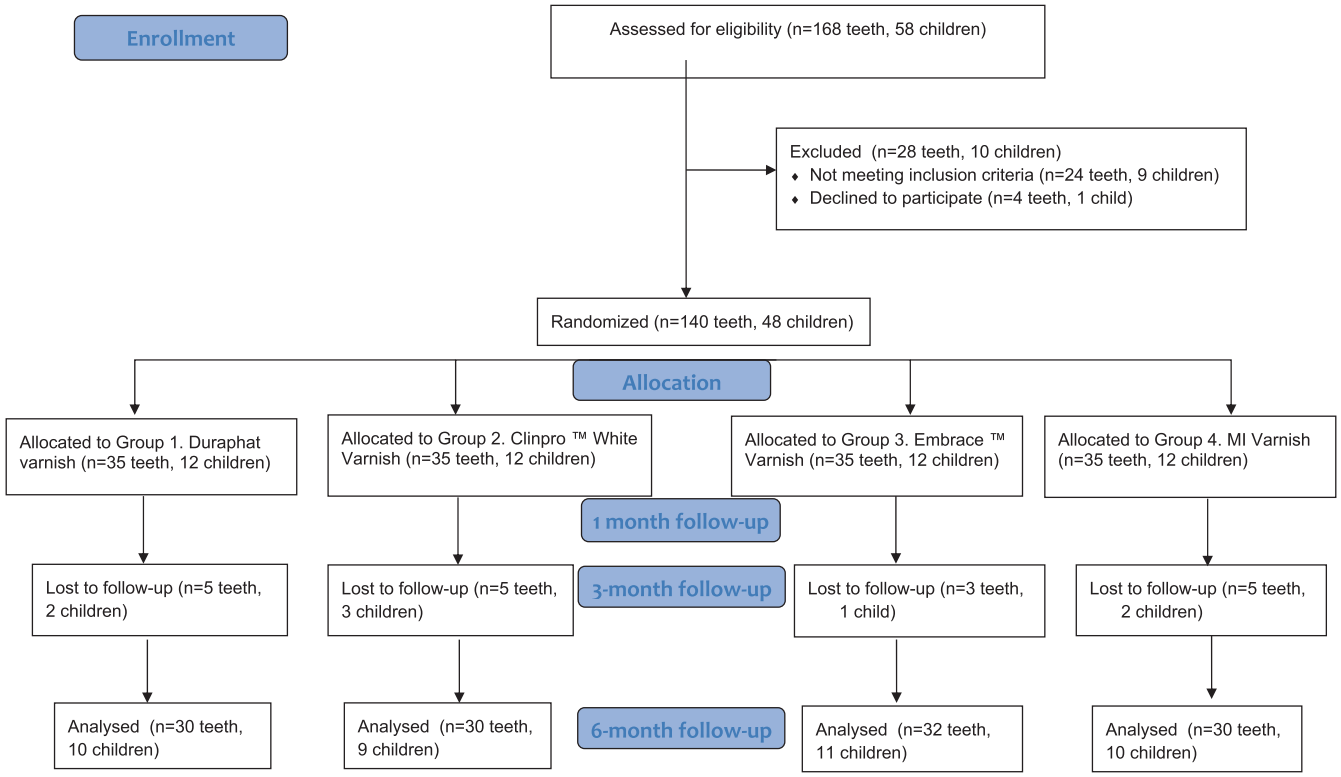

FIGURE 1 Flow diagram of the participants.

TABLE 2 Mean number of dmfs and mean age of children in each group.

Groups	*n* (teeth)	Mean age ± SD	Mean dmfs ± SD
Duraphat Varnish	30	7.2 ± 0.2	13.5 ± 5.5
Clinpro White varnish	30	6.5 ± 0.8	16.0 ± 4.2
Embrace Varnish	32	7.1 ± 0.6	18.0 ± 3.5
MI Varnish	30	6.8 ± 0.7	15.0 ± 6.2

NaF with TCP Varnish and NaF with CPP-ACP Varnish groups showed a significant decrease between baseline 1st, 3rd and 6th months ($p < 0.001$). In both groups, there is no significant difference in 1st month vs. 3rd month values only ($p = 0.914$ and $p = 0.923$ respectively).

In NaF with CXP Varnish group, there was a significant decrease in 3rd and 6th month values compared to baseline ($p < 0.05$). No statistically significant difference was observed in baseline vs. 1st month and 1st month vs. 3rd month values.

3.2 | Comparison between groups

There is no significant difference between the baseline LF values in all groups ($p > 0.05$).

At 1st month, there was no statistically significant difference between NaF with TCP.

Varnish and NaF with CPP-ACP Varnish groups and between NaF Varnish and NaF with CXP Varnish groups in terms of the decrease in LF values. However, remineralization effects of NaF with TCP Varnish and NaF with CPP-ACP Varnish groups have been found significantly greater than NaF Varnish and NaF with CXP Varnish groups ($p < 0.001$).

3rd month results show that NaF with CXP Varnish group significantly had the lowest decrease in LF values compared to other groups ($p < 0.05$).

At 6th month follow-up, there was a statistically significant difference between NaF with CPP-ACP Varnish and NaF with CXP Varnish groups, indicating that NaF with CPP-ACP varnish had a greater remineralization effect than NaF with CXP Varnish ($p < 0.05$). However, there was no statistically significant difference between the NaF Varnish (control) group and other groups.

NaF with TCP Varnish and NaF with CPP-ACP Varnish groups showed a similar decrease in LF values (remineralization effect) for all follow-up periods ($p > 0.05$).

3.3 | Changes in LF scores

Table 4 shows the distribution of LF scores at baseline, 1, 3 and 6 months for all groups.

When the LF scores of the groups were evaluated at 6-month follow-up, the percentages of '0' (LF value 0–13 regarded as healthy) score in the groups were as follows: NaF Varnish (%76.7) < NaF with

TABLE 3 Comparison of laser fluorescence measurements within and between groups according to different time intervals.

	DIAGNOdent Pen scores (mean ± SD)				
	Duraphat Varnish ($n=30$)	Clinpro White Varnish ($n=30$)	Embrace Varnish($n=32$)	MI Varnish ($n=30$)	*p-value*
Baseline	17.80 ± 5.46	16.46 ± 4.05	17.53 ± 4.69	16.36 ± 2.49	0.747
1 month	16.46 ± 6.68	11.06 ± 7.08	17.90 ± 7.28	10.40 ± 6.27	0.000*
3 months	12.30 ± 8.86	10.86 ± 8.25	15.50 ± 8.09	9.60 ± 5.42	0.007*
6 months	10.40 ± 6.99	9.10 ± 8.66	10.65 ± 4.97	6.60 ± 4.49	0.005*
p-value	$p_1=0.281$ $p_2=0.001$* $p_3=0.000$* $p_4=0.006$* $p_5=0.000$* $p_6=0.097$	$p_1=0.000$* $p_2=0.001$* $p_3=0.000$* $p_4=0.914$ $p_5=0.042$* $p_6=0.008$*	$p_1=0.697$ $p_2=0.033$* $p_3=0.000$* $p_4=0.063$ $p_5=0.000$* $p_6=0.000$*	$p_1=0.000$* $p_2=0.000$* $p_3=0.000$* $p_4=0.923$ $p_5=0.001$* $p_6=0.001$*	

p_1 = *p*-value for baseline vs. 1 month.
p_2 = *p*-value for baseline vs. 3 months.
p_3 = *p*-value for baseline vs. 6 months.
p_4 = *p*-value for 1 month vs. 3 months.
p_5 = *p*-value for 1 month vs. 6 months.
p_6 = *p*-value for 3 months vs. 6 months.
**Statistically significant*.

TABLE 4 Distribution of LF scores at baseline, 1, 3 and 6 months for all groups.

		LF score			
Time	***N***	**0**	**1**	**2**	**3**
Duraphat Varnish (SF group)					
Before treatment	30	0	24	6	0
1 month	30	9	14	6	1
3 months	30	22	3	2	3
6 months	30	23	4	3	0
Clinpro White Varnish (TCP group)					
Before treatment	30	0	26	4	0
1 month	30	21	6	2	1
3 months	30	24	2	3	1
6 months	30	25	3	2	0
Embrace Varnish (CXP group)					
Before treatment	32	0	24	8	0
1 month	32	13	6	11	2
3 months	32	15	9	6	2
6 months	32	25	6	1	0
MI Varnish (CPP-ACP group)					
Before treatment	30	0	27	3	0
1 month	30	24	3	3	0
3 months	30	25	3	2	0
6 months	30	29	0	1	0

CXP Varnish (%78.1) < NaF with TCP Varnish (%83.3) < NaF with CPP-ACP Varnish (%96.7).

No side effects or adverse events were observed throughout the study.

4 | DISCUSSION

Recently, non-invasive approaches to manage early carious lesions for preserving healthy tooth substance and preventing lesion progression have become important.[19,20] In this regard, fluoride has been shown to increase remineralization and fluoride varnishes have gained importance.[21] With the addition of different substances to fluoride varnishes, the effectiveness (including remineralization) of fluoride was intended to increase. In this regard, this is the first randomized clinical trial comparing the remineralization effect of NaF, NaF with TCP, NaF with CPP-ACP and NaF with CXP varnishes on newly erupted first permanent molars.

A laser fluorescence device (DIAGNOdent) was developed in the 1990s and used to aid with occlusal caries diagnosis. The amount of fluorescent light is measured by the photo-detector and the device displays a value between 0 and 99.[22] An increase in the fluorescence value indicates that the caries lesion progresses. In the present study, to monitor mineralization changes in newly erupted first permanent molars, laser fluorescence scanning method with a DIAGNOdent device was used. Similar to previous studies DIAGNOdent device was found to be an effective and useful tool for detecting early carious lesions and has a high sensitivity and acceptable specificity in monitoring mineralization changes.[22,23] In the present study, according to the manufacturer's instructions, values between 14 and 29 were included in the study indicating demineralization.

NaF Varnish (Duraphat) is a commonly used fluoride varnish that has been evaluated by similar studies and it increases the fluoride content of the enamel by releasing sufficiently high levels of fluoride ions.[16,18] In the present study, Duraphat, the gold standard fluoride varnish, containing NaF alone was used as a control group to compare other substances' additional effects on remineralization. Du et al.

(2012) have used NaF Varnish for the treatment of white spot lesions in their clinical study. They have reported that NaF Varnish provided a significant decrease according to LF values at the 3- and 6-month follow-up visits.[24] In the clinical study of Gozetici et al. (2019), NaF Varnish was reported to have a significant effect in remineralizing non-cavitated smooth surface caries lesions according to LF measurements at the end of 6 months.[25] Similar to previous studies, in the present study NaF Varnish showed a significant decrease in LF values indicating remineralization at the 3- and 6-month follow-up visits.

In a previous in vitro study evaluating the effect of different fluoride varnishes on remineralization of artificial enamel carious lesions; NaF, NaF with CPP-ACP, NaF with CXP, Enamel Pro and NaF with TCP Varnish were compared.[16] It was reported that all varnishes provided a remineralization effect, and NaF Varnish achieved a significantly higher remineralization effect on enamel carious lesions and NaF with TCP Varnish had a similar enamel remineralization effect as NaF Varnish. Similarly in the present study, at 6-month follow-up all the varnishes resulted in significant decrease and there was no significant difference between NaF Varnish and NaF with TCP Varnish. NaF with TCP Varnish contains functionalized TCP which is produced by functionalizing beta-TCP with silica. Mohd Said et al. (2017) reported that this may give the linking opportunities with hard-tissue defects under acidic conditions and can penetrate throughout enamel without attacking the interprismatic organic material that may give support for calcium, phosphate and fluoride uptake in demineralized lesions.

CPP-ACP is a novel milk-derived material that acts as a reservoir of bio-available calcium and phosphate, thereby helping in facilitating remineralization.[26] An in vitro study that compared NaF Varnish and NaF with CPP-ACP Varnish, found that NaF with CPP-ACP Varnish was more effective in reducing the depth of caries lesions around orthodontic brackets.[27] In previous studies, the synergistic effect of CPP-ACP with fluoride present in NaF with CPP-ACP Varnish had a higher release of calcium and fluoride ions than NaF Varnish and NaF with TCP Varnish[13] and was superior in protecting against enamel demineralisation.[28] Wierichs et al. (2018) compared the caries-preventive effect of NaF, NaF with TCP, NaF with CPP-ACP Varnish and silver diamine fluoride (SDF) in vitro and concluded that only NaF with CPP-ACP Varnish and SDF could remineralize artificial dentin caries-like lesions.[29] On the contrary in the present study, although the amount of LF value reduction is greater in NaF with CPP-ACP Varnish group, there is no superior significant remineralization effect of NaF with CPP-ACP Varnish compared to NaF Varnish. In previous in vitro studies, smooth surfaces of tooth samples were used for the evaluation of remineralization. In the present study, the remineralization effect was evaluated in the fissures of the teeth, which may be the reason for varying results from previous studies. Similarly in a previous clinical study, Llena et al. (2015) evaluated CPP-ACP paste (GC Tooth Mousse) versus fluoride varnish (Duraphat) on the remineralization of enamel white spot lesions by using DIAGNOdent and concluded that CPP-ACP is effective but not superior to fluoride varnish.[30] The authors stated that due to the difficulty in penetrating deep into the anatomy of pits and fissures, the efficacy of fluoride treatments may reduce.

In the present study, NaF with CXP Varnish was found to have a significant effect on remineralization but not superior to NaF Varnish. Similarly, Vongsavan et al. (2014) evaluated the combined effect of xylitol and fluoride varnish and concluded that the fluoride and xylitol varnish combination was beneficial for preventing enamel demineralization but no better than fluoride varnish alone in vitro.[31] Also Cardoso et al. (2014) and Mohd Said et al. (2017) have reported that the combination of fluoride and xylitol varnish has no significant benefit over varnish containing NaF alone.[16,32] In the present study at the end of 6 months, according to the mean LF values the amount of reduction (indicating remineralization) were as follows: NaF with CXP Varnish <NaF with TCP Varnish <NaF Varnish <NaF with CPP-ACP Varnish. The reason for the lowest remineralization effect of NaF with CXP Varnish may be explained as follows; the presence of fluoride may have inhibited diffusion of xylitol and reduced its remineralization effect.[32]

Although all children were initially given oral hygiene education, changes in their oral hygiene habits and diets may have occurred over a 6-month period. Therefore, at different time intervals, individual factors may have caused varying remineralization values. Although different LF value reductions in average values, all varnishes were found to be significantly effective in remineralization at the end of 6 months. It can be concluded that all these varnishes can be used in the treatment of early carious lesions and should be applied every 3 months in children with a high caries risk.

The limitations of the present study can be presented as follows: First, for the ethical reasons, there is no placebo group without a remineralizing agent. Therefore, if early caries lesions are not treated for 6 months, change in LF values could not be observed and a comparison could not be made with a placebo group. Second, for the ethical reasons again, laser fluorescence values greater than 29 (indicating dentine caries) were not included in the study. Also considering clinical examination, these teeth were treated using minimally invasive restorative procedures. Remineralization effect of the varnishes could not be evaluated on teeth with laser fluorescence values greater than 29. Third, one examiner did the LF measurements of the teeth included in the study. However, this limitation is thought to be eliminated by calibration and supervision with an experienced clinician.

In the present study, all of the varnishes resulted in significant decrease in LF measurements at the end of 6 months and there was no significant difference between control (NaF alone) group and other groups containing different substances. Therefore, the null hypothesis stating that 'different substances added to NaF varnishes provide greater remineralization effect than NaF alone' was rejected.

5 | CONCLUSION

1. At the end of 6 months fluoride varnishes with or without different substances are effective in remineralization of early

enamel lesions on newly erupted first permanent molars in high caries-risk children.
2. There was no significant difference between control (NaF alone) group and other groups containing different substances. While the highest effect was seen in NaF with CPP-ACP Varnish, the lowest effect was seen in NaF with CXP Varnish according to the mean LF values indicating remineralization.
3. It can be concluded that all these varnishes may be considered as a useful tool for the treatment of early carious lesions on newly erupted first permanent molars and should be applied every 3 months in children with a high caries risk to take advantage of remineralization efficiency.

6 | CLINICAL RELEVANCE

6.1 | Scientific rationale for study

This study was planned as a preventive measure as newly erupted first permanent molars are prone to caries in high caries-risk children.

6.2 | Principal findings

At the end of 6 months, fluoride varnishes with or without different substances are effective in remineralization of early enamel lesions on newly erupted first permanent molars in high caries-risk children.

6.3 | Practical implications

As a non-invasive approach, NaF varnishes with or without different substance has the potential to remineralize and should be applied every 3 months in children with a high caries risk. The addition of different substances to fluoride varnishes has no significant increase in remineralization effect.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Merve Erkmen Almaz https://orcid.org/0000-0001-6766-2023

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