ORIGINAL ARTICLE

CONTENTS

Casein phosphopeptide-amorphous- calcium phosphate's effect on enamel microhardness of teeth treated with nano silver in sodium fluoride solution

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ABSTRACT

Aim: To detect the effect of an experimental 0.7% nanosilver in sodium fluoride (NSSF) and compare it to that of 5% sodium fluoride (NaF) on demineralized teeth, also observes the impact of applying 10% Casein phosphopeptide-amorphous-calcium phosphate (CPP-ACP) on those groups and compares that to CPP-ACP's lone impact on demineralized teeth.

Materials and Methods: The sample consisted of 60 sound, premolar teeth without hypo-mineralization or cracks. They were divided into three groups following the formation of caries-like lesions using a Feather Stone pH cycle. Group No.1 was treated with NSSF, group No.2 was treated with NaF, and deionized water was used for Group No.3. All groups had two minutes of application time and were then stored for 24 hours in artificial saliva. After that, they were treated with CPP-ACP, for seven days twice a day.

Microhardness measurements were carried out four times: before any intervention, after the pH cycle, after 24 hours from the application of NSSF and NaF, and a final one after seven days from the application of CPP-ACP on the previous groups.

An XRF, XRD analysis, and particle size analyzer were used to confirm the nanosilver properties of the powder.

Results: There was a statistically significant increase in microhardness values ($P<0.05$) following CPP-ACP's application on teeth previously subjected to NSSF and NaF. The group that was subjected to deionized water before CPP-ACP's application revealed a statistically significant value ($P<0.001$).

Conclusions: CPP-ACP enhances the microhardness and, hence, the mineralization of teeth previously treated with NSSF and NaF solutions.

KEY WORDS: CPP-ACP, NSSF, 5% NaF, Microhardness

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INTRODUCTION

Dental caries is a widespread disease, still considered a burden to humans affecting their everyday lives. Its prevalence can be attributed to lifestyle or socioeconomic level, which is higher for permanent teeth in high socioeconomic areas and vice versa. However, caries level is noticeably lower among educated individuals [1]. Bacterial acids lead to degrading teeth's hard tissues, making it urgent to take early preventive measures to preserve the remaining tissues [2].

Dental fluoride has been used for decades to positively alter the constituents of dental plaque and saliva, increasing the minerals within them and consequently increasing the minerals diffusing to teeth [3].

Nanoparticles have been intensively investigated because of their unique characteristics. they have improved the field of preventive dentistry in tremendous ways by acting as drug delivery systems for treating and preventing dental diseases [4], and microbial biofilms prevention [5]. As nanomaterials, silver nanoparticles have a large surface area, which helps them adhere to the bacterial outer cell membrane and change the permeability and structure of the cells. Thus, at low concentrations, silver nanoparticles efficiently destroy bacterial cells [6].

Furthermore, the remineralizing effect of nanosilver, especially when it is combined with dental fluoride, has been identified by many studies.[7-8] Primary teeth with initial caries treated with fluoride varnish containing silver nanoparticles exhibited superior hardness compared to those treated with traditional NaF varnish when examined by diagnodent (detection of caries by laser fluorescence).[8] Also, nanosilver in sodium fluoride (NSSF) mouthwashes were found to be more effective than sodium fluoride (NaF)mouthwashes [9]. The exact mechanism is not clear, it is more likely to

be due to the fluoride component of NSSF helping to promote enamel remineralization and inhibiting the breakdown of enamel minerals in addition to the ability of nanosilver particles to penetrate deep in demineralized enamel due to their size and structure, which can consequently strengthen its hardness [7].

Previous animal studies have investigated milk and cheese for their anti-cariogenic effect, and have indicated that the actions of phosphoprotein casein and calcium phosphate components in cheese have been linked to this effect [10-11]. Recently, many in vitro and in vivo studies have shown that casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) has a remineralizing effect [12-13].

Due to their tiny size and naturality ionic, CPP-ACP complexes can penetrate subsurface enamel defects. Reports stated that in early carious lesions, the hydroxyapatite is surrounded by a crystalline cavity where the nano-complexes settle after diffusing through the holes into the lesion and releasing loosely bound calcium and phosphate ions [14].

Microhardness tests are frequently used to assess the hardness of teeth as well as to investigate changes in the physical characteristics of materials, such as density and hardness, or to determine their chemical composition. This study was assessed using the Vickers microhardness test which has been used in many previous studies.

AIM

To detect the effect of adding 10% CPP-ACP to teeth previously treated with either experimental NSSF or NaF solutions. And compare those to CPP-ACP's lone effect on demineralized teeth.

MATERIALS AND METHODS

SAMPLE SELECTION

The inclusion criterion was extracted permanent first premolar teeth, caries-free, without hypoplasia or fluorosis.

SAMPLE PREPARATION

The sample size was calculated to be 30 as determined by G power 3.1.9.7 (program writing by Franz-Faul, University of Kiel, Germany), so we doubled the sample size to increase the power of the study. A sample of 83 teeth was examined using x 6 dental loops (Univit, Italy); 60 of these satisfied the inclusion criterion. 10% thymol was used to store the teeth until used, to protect them from dehydration and any microbial growth. The sample was first washed with deionized water, subsequently cleaned with an ultrasonic cleaner (in an ultrasonic bath) and finally polished with non-fluoridated pumice powder. after that sof-lex discs (3M, St Paul, Minnesota, USA) were used to eliminate the fluoride-rich layer. The teeth were then coated with modeling wax (Schuler-Dental GmbH und Co. KG, Ulm, Germany) except for a (3X3mm) window at the center of the buccal surface [15].

CARIES LIKE LESION FORMATION

The 10-day Featherstone 1986 pH cycle was used to induce white spot lesions on our study sample,[16] which included applying the samples for six hours in a demineralization solution consisting of calcium chloride, acetic acid, and phosphate chloride, of about 1.0 mM/L, 0.075 M/L, and 2.0 mM/L respectively. The pH was adjusted to 4.3 at 37 °C.

This was followed by cleaning with deionized water for 60 sec and the application of the sample for 17 h in a remineralization solution consisting of potassium phosphate, calcium nitrate, and potassium chloride of about 0.9mM/L, 105 mM/L and 150 mM/L, respectively. The pH was adjusted to 7 at 37 °C. The pH was checked every day for solutions with the use of a pH meter [17].

NANOSILVER IN SODIUM FLUORIDE SOLUTION PREPARATION

The concentration of the nanosilver to be used was determined by previously made pilot study containing varying concentrations of NSSF.

A wight dilution percent was used to prepare 0.7 % nanosilver powder (supplied by Hongu International Group. Ltd, China) in 5% sodium fluoride solution by applying 0.7 gm of nanosilver powder to a volumetric flask, then adding 5 gm of sodium fluoride powder (supplied by Thomas Baker (Chemicals) Pvt. Ltd. India) and dissolve it in deionized water of 100 ml. An ultrasonic homogenizer (model UP200Ht, Hielscher, Germany) was then used and stirred until a colloidal suspension was formed [18].

APPLICATION OF REMINERALIZATION AGENTS

60 upper premolars were used in this study as shown in fig.1. They were subjected to the pH cycle, and then, to the application of remineralizing agents which occurred in two steps as follows:

1st step: The sample was divided into three groups, 20 teeth each:

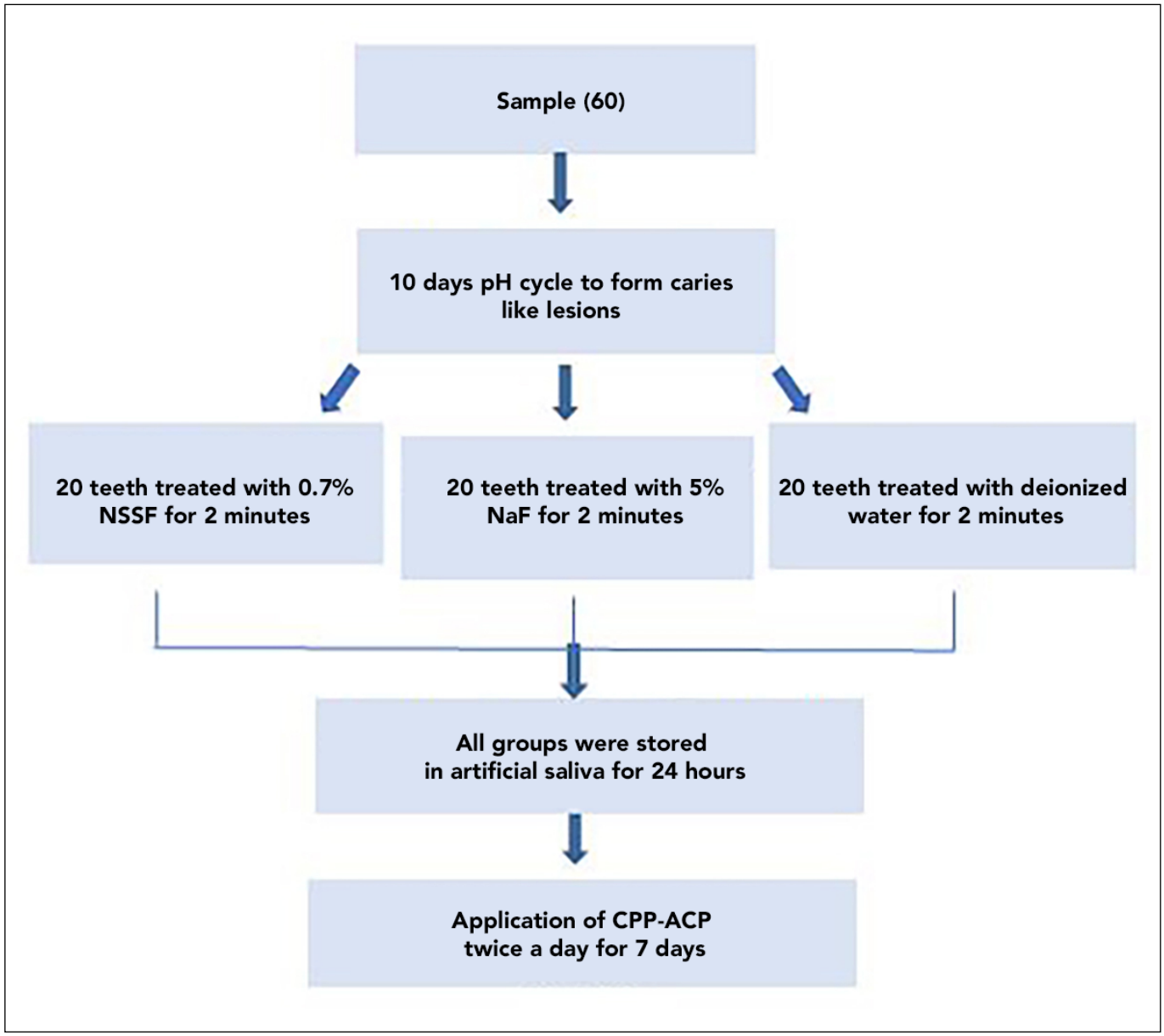

Fig. 1. Study design.

Group No.1: The NSSF group was treated with 0.7 % nanosilver in a 5% sodium fluoride solution for 2 minutes using a micro brush.

Group No.2: The NaF group was treated with 5% sodium fluoride solution for 2 minutes using a micro brush.

Group No.3: The control group was treated with deionized water for 2 minutes using a micro brush.

The teeth of all groups were washed with deionized water for 60 seconds and stored in artificial saliva for 24 hours.

2nd step: all teeth were subjected to 7 days application of 10 % CPP-ACP(GC mousse, Tokyo), twice a day with the use of an insulin syringe, by applying the paste in the syringe and disposing 0.2 ml of the paste for each tooth. The teeth were then rubbed with a micro brush, the past was left on the specimens for 3 minutes then wiped with gauze, washed with deionized water for 60 seconds, and stored in artificial saliva separately in an attempt to mimic the oral environment.[19]

ASSESSMENT OF SURFACE MICROHARDNESS (SMH):

Four microhardness readings were achieved with the use of the Vickers microhardness test by applying a load of 300 grams for 15 seconds (machine instruction); three indentations at the center of the enamel surface were made.

The measurements were as follows: one at baseline before any intervention, the second after subjecting the teeth to the pH cycle, the third after applying nanosilver in sodium fluoride and sodium fluoride and a final measurement after applying CPP-ACP, as shown in fig.2. The microhardness measurement was immediately taken at the end of each stage.

To confirm the nanosilver properties of the powder, X-ray fluorescence (XRF) and X-ray diffractometer (XRD) and particle size analyzer have been performed.

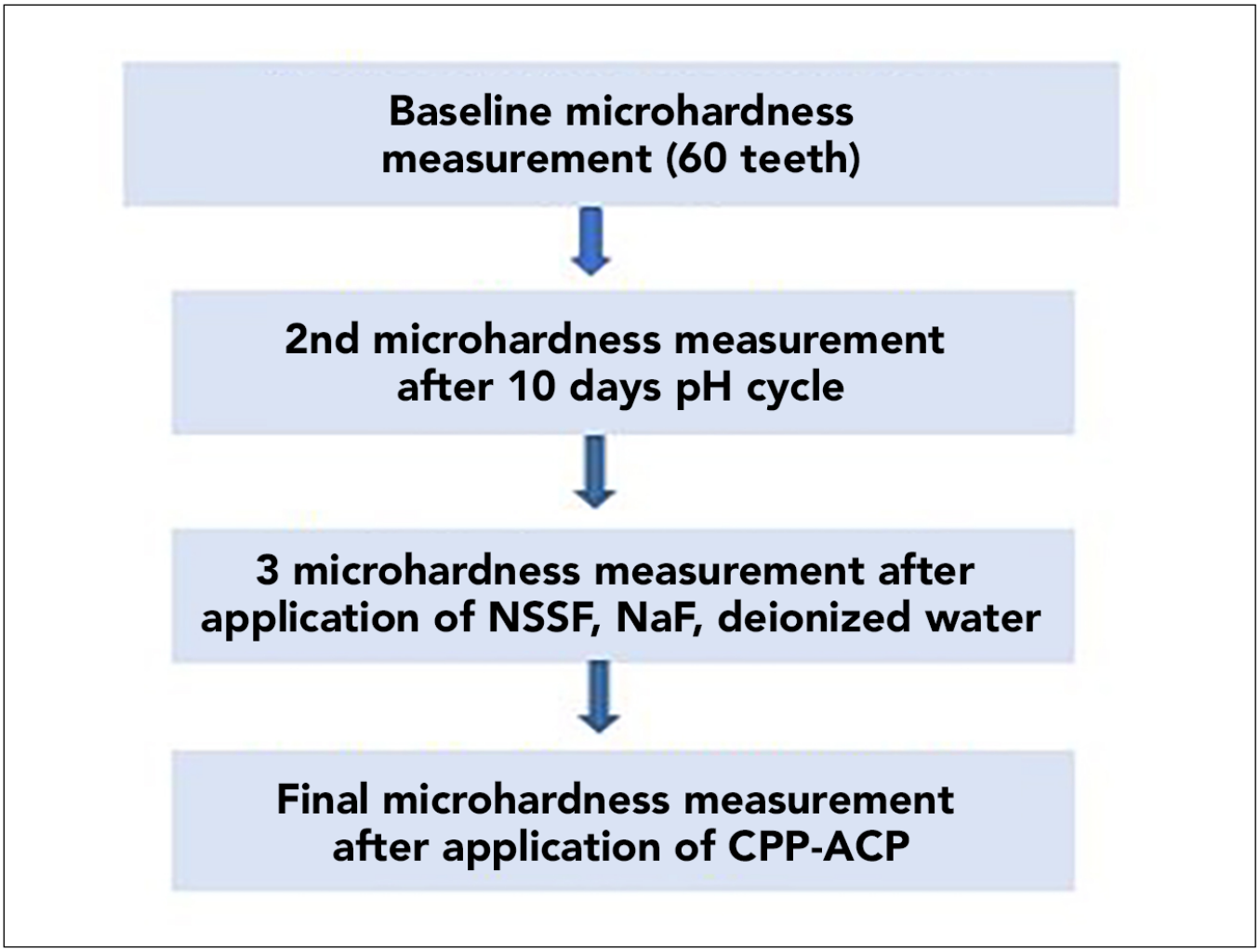

Fig. 2. Microhardness measurements sequence.

STATISTICS

The analysis of the data was performed with the use of a statistical package for the social sciences software (SPSS) the data were analyzed using;

1. Shapiro–Wilk analysis (to check the normality of the data)
2. Descriptive analysis
3. Onaway (ANOVA)
4. LSD.

ETHICS APPROVAL

Ethical approval was taken from The MUCOD Human Research Ethics Committee, study number (MUPRV005).

RESULTS

WRF AND XRD ANALYSES

A. XRF analysis showed high-purity powder containing 98.4% silver.

B. XRD analysis was used to examine composition, structure of crystals, and the orientation of the powder. The result showed that the powder had distinct diffraction peaks which conforms to the conventional power diffraction pattern established by the Joint Committee on Powder Diffraction Standards (JCPDS).

A particle size analyzer was used to confirm the nano size of the nanosilver solution showed that the effective size of the particles was (39.2 nm), polydispersity was (0.272).

ENAMEL MICROHARDNESS RESULTS

The descriptive analysis of teeth in the NSSF group (group No.1) before and after CPP-ACP application, is shown in Table 1. While that of the NaF group (group No.2) is shown in Table 2. Meanwhile, Table 3 represents the descriptive analysis of the control group (group No.3) before and after CPP-ACP application.

ANOVA test that shows the degree of freedom and significance. The LSD test that shows the mean defer-

Table 1. Descriptive analysis of the NSSF group (group No.1) before and after the application of CPP-ACP

Stage	Min	Max	Mean	Std. deviation
Baseline	282.3	383.3	326.030	28.1003
Demineralization	48.3	168.0	113.940	33.9648
NSSF	100.3	258.6	199.255	47.4818
CPP-ACP	118.0	302.6	235.210	52.1675

Table 2. Descriptive analysis of the NaF group (group No.2) before and after the application of CPP-ACP

Stage	Min	Max	Mean	Std. deviation
Baseline	295.0	385.0	327.795	22.9774
Demineralization	54.6	193.6	119.115	36.9409
NaF	74.0	302.0	195.910	51.8414
CPP-ACP	115.3	297.0	230.41	46.9890

Table 3. Descriptive analysis of the deionized water group (group No.3) before and after the application of CPP-ACP

Stage	Min	Max	Mean	Std. deviation
Baseline	281.6	378.6	327.96	27.203
Demineralization	55	190.1	113.19	36.454
Deionized	58	194	121.15	36.352
CPP-ACP	98	232	169.92	40.294

Table 4. ANOVA and LSD analysis of the NSSF group (group No.1) before and after the application of CPP-AC

Type Stage	ANOVA			LSD		
	F -value	P -value	Degree of freedom	Pairwise comparisons	Mean difference	P -value
Baseline (1)	89.864	<.001	3	1vs 2	212.090	<.001
Demineralization (2)				1vs 3	126.775	<.001
NSSF (3)				1vs 4	90.825	<.001
CPP-ACP (4)				2vs 3	85.315	<.001
				2vs4	121.256	<.001
				3 vs 4	35.950	<.05
Statistical significant (p<0.05)						

ence and significance of each step of each group are shown in Tables (4-7).

The result revealed a statistical significance increase (P<.05) in microhardness values of samples treated in the CPP-ACP step compared to that of the first remineralizing step for NSSF and NaF groups, as shown in Tables 4 and 5. Moreover, a statistical significance increase (P<0.001) in microhardness values of samples treated in the CPP-ACP step compared to that of the first remineralizing step for the control group, as shown in Table 6.

LSD analysis showed a non-significant increase (P>.05) between the CPP-ACP stage in the NSSF group and its effect in the NaF group, as shown in Table 7.

DISCUSSION

Recently, CPP-ACP has shown to be a successful non-invasive method for caries lesion prevention. Several investigations have demonstrated the effectiveness of CPP-ACP in remineralizing enamel lesions [20-21].

An inverse correlation exists between the saturation of phosphor and calcium ions and the onset of dental caries. Rajendran et al. suggested that CPP-ACPF and CPP-ACP and added fluoride varnish were more effective than CPP-ACP alone [22].

This investigation used CPP-ACP as a second step for mineralizing teeth previously treated with 0.7% NSSF or 5% NaF or deionized water to assess its efficacy on the enamel surface through the Vickers microhardness test.

Table 5. ANOVA and LSD analysis of the NaF group (group No.2) before and after the application of CPP-ACP

Type stage	ANOVA			LSD		
	F -value	P -value	Degree of freedom	Pairwise comparisons	Mean difference	P -value
Baseline (1)	88.291	<.001	3	1vs 2	208.680	<.001
Demineralization (2)				1vs 3	131.885	<.001
NaF (3)				1vs 4	97.385	<.001
CPP-ACP (4)				2vs 3	76.7950	<.001
				2vs4	111.295	<.001
				3 vs 4	34.500	<.05
Statistical significance (P< 0.05)						

Table 6. ANOVA and LSD analysis of the deionized water group (group No.3) before and after the application of CPP-ACP

Type Stage	ANOVA			LSD		
	F -value	P -value	Degree of freedom	Pairwise comparisons	Mean difference	P -value
Baseline (1)	58.921	<.001	3	1vs 2	214.760	<.001
Demineralization (2)				1vs 3	206.805	<.001
Control (3)				1vs 4	158.040	<.001
CPP-ACP (4)				2vs 3	7.955	>0.5
				2vs4	56.720	<.001
				3 vs 4	48.765	<.001
Statistical significance (P<0.05)						

The results revealed that the mean microhardness values at the baseline stage of all groups were similar, which indicates that the teeth were sound and fit for the study. The mean microhardness values of the demineralization stage of all groups were also similar, with no significant difference between groups, ensuring that the pH cycle used in this study effectively created caries-like lesions, as has been shown by other studies that have used it before [17,23]. Following the application of the first remineralization agent on each group (NSSF for group No.1, NaF for group No.2, and deionized water for group No.3), the results showed a statistically significant increase between the demineralization stage for NSSF and NaF groups (P <0.001), and remineralization stage of those group, ensuring minerals transportation to the defective enamel.

The difference between the demineralization stage and the deionized stage in the control group was without significant increase (P>.05), ensuring the non-mineralizing capacity of deionized water.

The incorporation of nanosilver compound into fluoride has recently been studied as a treatment of early carious lesions. In a study conducted on preschool children, Quritum M et al. Found that NSSF exhibited superior efficacy in combating caries among preschool children [24].

Table 7. ANOVA test and LSD between groups after CPP-ACP application

Type Stage	ANOVA			LSD		
	F -value	P -value	Degree of freedom	Pairwise comparisons	Mean difference	P -value
CPP-ACP in the NSSF group (1)				1vs 2	4.795	>.05
CPP-ACP in NaF group (2)	12.220	<0.001	2	1vs 3	65.290	<.001
CPP-ACP in control group (3)				2vs 3	60.495	<.001
Statistical significance (P<0.05)						

Contrary to our study, Nozari et al. concluded in their study that the surface microhardness of enamel was considerably greater following nano-silver fluoride treatment compared to groups treated with fluoride varnish and nano-hydroxyapatite [25] this could be due to different preparation methods for NSSF and different types of teeth used since deciduous teeth were used in their study while permanent premolars were used in the current study.

Our results revealed that the mean microhardness of teeth treated with NSSF and NaF were (199.255 and 195.910) respectively, which reflects a close resemblance in their effect. An investigation conducted by Kooshki et al. using premolar teeth agreed with our results that there was no difference in enamel microhardness between groups treated with different concentrations of NSSF and NaF varnish [26].

Following the application of CPP-ACP on each group, the results showed a significant increase (P<0.05) between the CPP-ACP stage and NSSF and NaF stages, which ensures that the CPP-ACP has performed an additive remineralization effect that led to the increase in microhardness of the teeth in these two groups.

The results also showed a high significant increase (P<0.001) between the remineralization stage and the CPP-ACP stage of the deionized group, revealing the strong effect the CPP-ACP performed alone. These results align with data from earlier studies indicating that CPP-ACP possesses a preventive capability against dental caries and enhances the remineralizing action of NaF [27-28].

Adhering to the guidelines provided by the manufacturer, the duration of CPP-ACP application in this investigation was 3 minutes. Pulido et al. proposed that extended treatment durations could be necessary to identify and monitor changes in calcium and phosphorus deposits [29]. According to AL-Mullahi et al., it was found that increasing the application period of CPP-ACP to 30 minutes might enhance the effectiveness of enamel remineralization further. Due to its ability to attach to the bacterial biofilm on the tooth surface, CPP-ACP causes circumstances of supersaturation. However, the lack of biofilm in in-vitro investigations may hinder CPP-ACP from fully exerting its impact [30].

Based on the current study results, the hypothesis declaring that CPP-ACP's effect on NSSF-treated teeth has greater microhardness than that of only NSSF treated teeth was accepted, since there was a statistically significant increase (P<0.05) in microhardness values after the application of CPP-ACP on NSSF treated teeth.

The possible limitations of this study would be the short duration of CPP-ACP application, lack of dental biofilm, individual's dietary patterns, and oral cleaning routines, which may result in different results.

Our study revealed that the final microhardness values of the groups that were treated with NSSF and NaF before being treated with CPP-ACP were closest to the baseline microhardness values. The final microhardness values of these groups were so close to each other but much higher than that of CPP-ACP alone, reflecting the extra mineralization CPP-ACP supply when used after other remineralizing materials.

CONCLUSIONS

This study confirmed the successful remineralizing potentials of CPP-ACP when used following 0.7% nanosilver in sodium fluoride and 5% sodium fluoride solutions. CPP-ACP gives an extra mineralization effect even when used for a short duration. Within the limitation of the study, we recommend the daily use of CPP-ACP, whether alone or subsequent to other types of professional remineralization, since it is not costly, easily accessible, and has a remarkable remineralizing effect. Several investigations are required to detect CPP-ACP's impact on extended duration alone and subsequent to NSSF and NaF solutions.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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