

Article

Activity of Fluoride Varnishes Containing Micrometric or Nanosized Sodium Trimetaphosphate against Early Enamel Erosive Lesions *In Vitro*

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Abstract: This study aimed to assess the effects of fluoridated varnishes supplemented with micrometric or nanosized sodium trimetaphosphate (TMPmicro or TMPnano, respectively) against enamel softening in an early erosive model *in vitro*. Bovine enamel blocks (with mean surface hardness [SH] between 330.0 and 380.0 kgf/mm²) were selected and randomly assigned according to their SH ($n = 8$) into the following groups: Placebo (no fluoride/TMP; negative control), 5% NaF (positive control), 5% NaF + 5%TMPmicro, 5% NaF + 2.5%TMPnano and 5% NaF + 5%TMPnano. Blocks received a single application of the varnishes and were immersed in artificial saliva (6 h). Thereafter, the varnishes were removed and the blocks were subjected to four individual erosive challenges (1 min, citric acid, 0.75%, pH = 3.5, under agitation); SH was determined after each challenge. Data were subjected to ANOVA and Student–Newman–Keuls’ test ($p < 0.05$). Overall, the highest %SH loss was observed for the Placebo, followed by 5% NaF, 5% NaF + 5% TMPmicro, and both varnishes containing TMPnano, without significant differences between 2.5% and 5% TMPnano. It was concluded that TMP enhanced the effects of a 5% NaF varnish against enamel softening in an early erosive model *in vitro*, with an additional benefit from the use of nanoparticles over microparticles.

Keywords: fluoride varnish; polyphosphates; tooth erosion; topical fluorides; dental enamel



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1. Introduction

Dental erosion is defined as the loss of hard dental tissues caused by a chemical process without bacterial involvement [1]. Briefly, the initial stage of erosion involves the softening of the enamel, marked by partial dissolution of the tooth surface without material loss. Subsequently, the association with mechanical forces results in material loss (i.e., erosive tooth wear), leaving behind a softened enamel layer [1]. Therefore, the effectiveness of a treatment both in reducing enamel softening and boosting the rehardening of the softened enamel is crucial in preventing material loss [2].

Despite the unquestionable benefits of fluoride on caries control, conventional fluoride therapies exert limited effects on the prevention of tooth erosion. To protect enamel from erosion, the calcium fluoride-like layer deposited on enamel should be sufficiently thick, creating a physical barrier, as during the erosive process, demineralization happens primarily in the enamel’s outermost layers, which is the reason why the calcium fluoride precipitates become more soluble in the face of the acid challenges. The limited action of fluoride against dental erosion has prompted studies assessing the effects of novel therapeutic strategies using alternative agents in association with fluoride, aiming at

improving its effectiveness [3–5]. Among the options available, sodium trimetaphosphate (TMP) and inorganic cyclophosphate salt, incorporated into fluoride-containing products, have been shown to promote a synergistic protective effect against enamel erosive wear [6]. Interestingly, recent data have demonstrated that the use of nanosized TMP (TMPnano) can further enhance the protective effects of micrometric TMP, when associated with fluoride, against enamel erosive wear [7,8]. Shortly, TMP adsorbs onto the enamel surface, creating a barrier that hinders acid diffusion. This process promotes the development of a more stable mineral structure, affecting mineral dissolution [6–8].

Considering the options of fluoride therapies for professional application, dental varnishes have been used in dentistry for several decades, and stand out due to their ease of application, patient acceptance, and safety [9–11]. These products have been demonstrated to be effective for caries prevention as well as for treating or arresting carious lesions, especially in children and adolescents [12–15]. In brief, dental varnishes allow for the application of high fluoride concentrations at specific sites using a thin layer of the product (i.e., a polymeric matrix in which fluoride is embedded), which hardens in contact with saliva, then slowly releases the actives over time. Within this context, despite the use of high fluoride concentrations raising concerns due to the potential for increased toxicity [16], varnishes are regarded as a safer preventive alternative than other clinically applied fluoride modalities (e.g., gels), even for young children that use fluoridated dentifrice regularly, given that very low amounts of the products are applied [17,18].

Although *in vitro* and *in situ* studies attest the protective effects of fluoride varnishes supplemented with TMPs on advanced enamel erosive wear [6–8], no evidence is available on the effects of such formulations on the early stages of enamel erosion. The investigation of such effects, using both micrometric and nanosized particles of this polyphosphate, could provide relevant insights into the mechanisms by which these formulations have led to superior protective effects in comparison with TMP-free counterparts.

Based on the above, this study aimed to investigate the impact of fluoridated varnishes enriched with micrometric or nanosized TMP on initial enamel erosion. The null hypotheses of the study were that (1) the incorporation of TMP to sodium fluoride (NaF) varnishes would not enhance its effectiveness over a commercial TMP-free product on the prevention of enamel softening in an initial enamel erosive model *in vitro*, and (2) TMP particle size would not influence the effects of the phosphate incorporated to the varnish.

2. Materials and Methods

2.1. Experimental Design

Bovine enamel blocks ($n = 40$; 8 blocks per group) were selected after surface hardness analysis (SH). Blocks with mean SH between 330.0 and 380.0 kgf/mm² were included in the study to standardize the average hardness of the blocks, preventing wide variations that might result from specimen selection. The blocks were then randomly divided into 5 experimental groups ($n = 8$) according to the varnishes to be tested: Placebo (no fluoride/TMP; negative control; PLA); 5% NaF (positive control; 5%NaF); 5% NaF/5% micrometric TMP (5%NaF/5%TMPmicro); 5% NaF/5% nanosized TMP (5%NaF/5%TMPnano), and 5% NaF/2.5% nanosized TMP (5%NaF/2.5%TMPnano). Blocks were treated once with the varnishes and immersed in artificial saliva (6 h). The varnishes were then removed from the enamel surface and the blocks and subjected to individual erosive challenges (four erosive challenges/1 min each); SH was again determined after each challenge [19]. Figure 1 summarizes the study design.

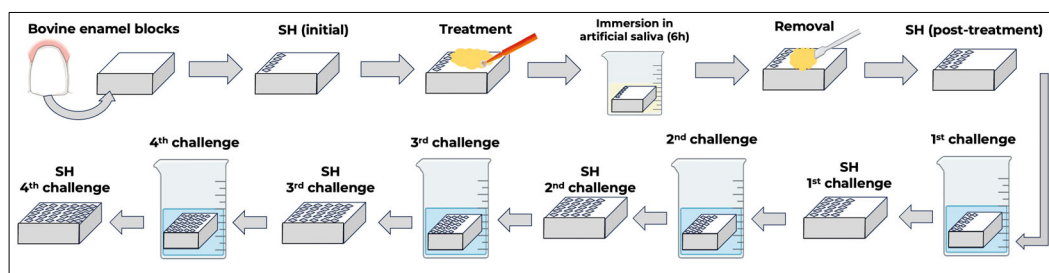


Figure 1. Schematic diagram illustrating the experimental design of the study. SH = surface hardness. The erosive challenges were performed by immersing the blocks in citric acid (0.75%, pH = 3.5, 1 min for each challenge).

2.2. Synthesis and Characterization of Nanosized TMP Particles

For this study, the varnishes utilized were identical to those employed in the research conducted by Paiva et al. [8]. The nanosynthesis process involved the transformation of commercial micrometric sodium trimetaphosphate, briefly described as follows: commercial sodium trimetaphosphate (70 g, $\text{Na}_3\text{O}_9\text{P}_3$, Aldrich Chemistry, St. Louis, MO, USA, purity $\geq 95\%$ CAS 7785-84-4) was ball milled using 500 g of sintered zirconia spheres of 2 mm diameter in 1 L of isopropanol in a polypropylene bottle. After 48 h, at a grinding speed of 1200 rpm, powders were separated from the alcoholic medium, dried at 60 °C, and ground in a mortar [8]. The TMPnano-containing varnishes were featured with TMP nanoparticles with an approximate size of 22.7 nm, which was evaluated by scanning electron microscopy (SEM), using a Philips XL-30 FEG equipment (Philips, Amsterdam, The Netherlands). The structure of these nanoparticles was evaluated using a Shimadzu XRD 6000 (Kyoto, Japan) with a CuK radiation source ($\lambda = 1.54056 \text{ \AA}$), voltage of 30 kV and current of 30 mA. The crystalline structure of the nanoparticles was found to be consistent with that of conventional TMP [8].

2.3. Varnish Formulation and Determination of Fluoride in Products

The varnishes were produced by SS White Dental Products (Rio de Janeiro, RJ, Brazil), and contained the following components: colophony, ethyl cellulose, tolu balsam, beeswax, toluene sulfonamide, vanillin, saccharin, and ethanol. The fluoride-containing varnishes presented 5% NaF (Merck, Darmstadt, Germany). To the phosphate-containing products, sodium trimetaphosphate (Aldrich Chemistry, China) was added at 5% (micrometric or nanosized) or 2.5% (nanosized). The fluoride concentrations in the varnishes were determined using a fluoride ion-specific electrode (9609 BN, Orion, Waltham, MA, USA) coupled with an ion analyzer (Orion 720 A+) and calibrated with standards ranging from 2.0 to 32.0 μg fluoride/mL, as previously described [6,20]. The mean (standard deviations) fluoride concentrations of the varnishes were 433.6 (33.5), 21,378.8 (708.1), 20,154.0 (326.9), 20,063.5 (301.7), and 20,154.0 (326.9) μg fluoride/g respectively for the Placebo; 5% NaF; 5% NaF + 5% TMPmicro; 5% NaF + 2.5% TMPnano; and 5% NaF + 5% TMPnano, as previously described by Paiva et al. [8].

2.4. Preparation of Enamel Blocks

As bovine teeth were obtained from the *post mortem* disposals of animals raised for commercial slaughter (Article 1, paragraph 3, Law No. 11.794/08, of 8 October 2008, Brazil), and animal experimentation is defined as procedures conducted on living animals (Article 3, Law No. 11.794/08, of 8 October 2008, Brazil), this study did not require prior approval from the Ethics Committee for the Use of Animals. Enamel blocks (4 mm $\times$ 4 mm) were obtained from bovine incisors and were serially polished. The surface hardness (SH) was determined as follows: one indentation was made at a distance of 1000 μm (Knoop diamond, 500 g, 10 s, Shimadzu HMV-2000) [20] from the central region of the blocks' surface to facilitate indentation localization on subsequent measurements. At a distance of

200 µm from the right vertex of this greater indentation, five indentations, separated by a distance of 100 µm, were made (Knoop diamond, 25 g, 10 s, Shimadzu HMV-2000).

2.5. Treatment with the Varnishes and Erosion Cycles

The varnishes were applied with a microbrush on each block only once. The blocks were immersed in 4 mL of artificial saliva (1.5 mmol·L⁻¹ Ca(NO₃)₂·4H₂O; 0.9 mmol·L⁻¹ NaH₂PO₄·2H₂O; 150 mmol·L⁻¹ KCl; 0.1 mol·L⁻¹ Tris buffer; pH 7.0; unstirred, 37 °C) for 6 h. The varnishes were then gently removed with a blade and acetone [10]. The erosive challenge consisted of individually immersing each enamel block in 4 mL of citric acid (0.75%, pH = 3.5; Synth, Diadema, SP, Brazil) under agitation (100 rpm) for 1 min at room temperature, representing erosive conditions commonly found in extrinsic enamel erosion caused by citric fruits and sodas. Thereafter, the blocks were washed with deionized water for 20 s. In total, four erosive challenges were performed. Surface hardness (SHf) measurements were carried out after each erosive challenge to calculate the percentage of surface hardness change (SHC = [(SHf – SHi)/(SHi)] × 100) after 1, 2, 3, and 4 min of challenge [6,21]. The acid challenging was performed to evaluate the cumulative effects of short-term, consecutive exposures to erosive condition. In this way, the effects of the test products could be assessed within each timepoint, allowing us to verify the immediate and sustained effects on enamel softening.

2.6. Statistical Analysis

The sample size was calculated based on a pilot study conducted with 4 blocks/group, according to which 7 blocks would be required to detect statistically significant differences in mean percentage of surface hardness change of blocks treated with a Placebo (no fluoride or TMP) and a 5% NaF varnish (mean difference = 5.79, standard deviation = 1.5), considering a power of 80% (α = 0.05). Due to the possibility of losses during the processing of the specimens, 8 blocks were included in each group.

For the statistical analysis, SigmaPlot software for Windows (version 12.0) was used and the significance limit was set at 5%. Data did not present normal (Shapiro–Wilk’s test) and homogeneous (Cochran’s test) distribution. For surface hardness at baseline (prior to the first acid challenge), data were submitted to Kruskal–Wallis test. Data on the percentage of surface hardness change were submitted to 2-way, repeated-measures ANOVA, considering the type of varnish and time of exposure to acid as variation factors. Student–Newman–Keuls’ test was used as the *post hoc* test for ANOVA.

3. Results

The median (interquartile range) of surface hardness at baseline was 354.4 (349.3–366.6) kg/mm², considering all groups. The lowest median was 354.0 (350.9–366.6) and the highest median was 355.8 (352.5–363.6), without statistically significant differences among the groups prior to the first acid challenge ($H = 0.439$, $p = 0.979$).

Statistically significant differences were observed among the varnishes ($F = 366.0$, $p < 0.001$), times of exposure to acid ($F = 655.3$, $p < 0.001$), and for the interaction between these variables ($F = 109.1$, $p < 0.001$). At 1 min of exposure to acid, the highest surface hardness change was observed for the Placebo, followed by 5% NaF and the TMP-containing varnishes ($p < 0.05$), without differences among the latter regardless of the type of particle (micro or nano) or TMP concentration (2.5 or 5%). At 2, 3, and 4 min, statistically significant differences were observed among the Placebo, 5% NaF, 5% NaF/5% TMP micro, and both varnishes containing TMP nano; however, there were no statistically significant differences between 2.5% and 5% TMPnano containing varnishes. Also, at these timepoints, the 5% NaF group demonstrated statistically significantly lower enamel softening compared to the Placebo group, while the 5% NaF/5% TMP micro treatment showed a superior effect to 5% NaF alone. Furthermore, TMPnano treatment resulted in the smallest amount of enamel softening, regardless of concentration. As for the durations of exposure to acid, statistically significant differences were observed among all times for all varnishes tested (Figure 2).

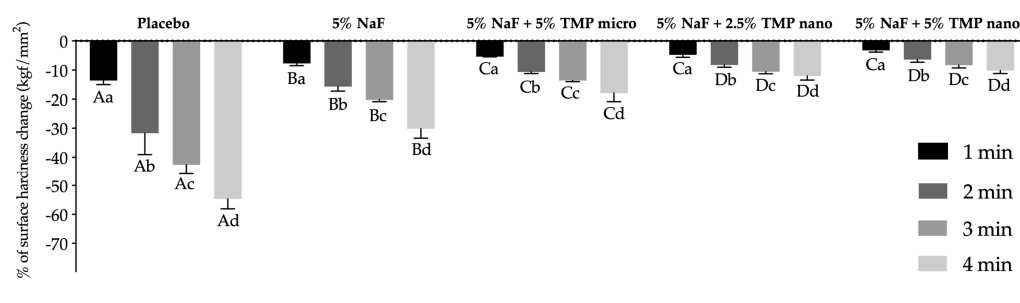


Figure 2. Mean percentage of surface hardness change according to the varnishes applied and the time of exposure to citric acid. Uppercase and lowercase letters indicate significant differences among the varnishes (at each individual time point) and among the times after exposure to acid (within each varnish), respectively. Two-way, repeated measures ANOVA and Student–Newman–Keuls test ($p < 0.05$, $n = 8$) were performed. Bars indicate standard deviations of the means.

4. Discussion

The use of fluoride in different modalities has been widely regarded as a successful method of caries control, and includes application of silver diamine fluoride [22], tooth-pastes [23], mouthrinses [24], and consumption of fluoridated drinking water [25]. Among the modalities, dental varnishes stand out due to their effectiveness, lack of substantial side effects, and high acceptability [10–12]. While caries prevalence and incidence have decreased worldwide in recent years [26], dental erosion has become increasingly prevalent due to shifts in lifestyle and eating habits. Within this context, several strategies have been investigated in order to prevent, minimize, or reverse enamel erosive lesions, among which topical fluoride application at high concentrations (e.g., dental varnishes) has been shown to be beneficial, despite a limited effect [4,5,16]. The present study demonstrated that (1) TMP significantly increases the effect of a conventional 5% NaF varnish against enamel softening in an initial enamel erosive model *in vitro*, and (2) the use of nanoparticles promoted significantly additional effect in comparison to conventional or micrometric particles. Thus, the study's null hypotheses were rejected.

The protective effects of TMP incorporated into fluoridated varnishes against erosive or erosive and abrasive enamel wear have been previously investigated [6] using an artificial resin-based formulation containing 2.5% NaF. It was demonstrated that the experimental TMP-containing varnish exhibited significantly higher anti-erosive effects compared to a commercial TMP-free product with 5% NaF. Subsequently, a colophony-based varnish containing TMP was evaluated for enamel remineralization [27]. The results showed that the fluoride varnish with 5% TMP provided superior remineralizing effects compared to its polyphosphate free counterpart, prompting further testing on dentin erosion. In that case, varnishes containing either 2.5% or 5% NaF enriched with 2.5% or 5% TMP promoted significantly greater protective effects, regardless of the TMP concentration, against dentin erosive or erosive and abrasive wear when compared to the varnishes containing only fluoride [28]. In brief, these promising findings are attributed to TMP's ability to adsorb onto enamel, creating a protective surface layer that reduces acid diffusion [29]. When associated with fluoride, TMP also favors the retention of calcium and/or fluoride ions and species, which play a relevant role in demineralization and remineralization processes [27].

In line with the aforementioned findings, the addition of TMP to a NaF colophony-based varnish has shown promising protective effects against enamel erosion, similar to those observed with artificial resin-based varnishes. In a recent study, Paiva et al. [8] demonstrated *in vitro* that varnishes containing TMP (at 5% NaF) significantly enhanced protection against erosive tooth wear. This protective effect was further enhanced by incorporating polyphosphate as nanoparticles, as varnishes with nanosized TMP exhibiting reduced enamel wear compared to varnishes containing microparticulate TMP or conventional fluoride varnishes (i.e., varnishes containing only fluoride). This trend was attributed to

the higher contact surface of nanoparticles, as well as the higher percentage of atoms on the surface compared to micrometric ones, which enhances their reactivity [30,31]. The lower particle size of TMPnano might also be associated with increased interaction with the varnish matrix, which may result in lower mobility to the oral environment [8,32]. Despite the promising trends of the effects of TMP-loaded varnishes in both particle sizes using a model assessing advanced erosive or erosive and abrasive lesions, the effects of these varnishes assessing initial erosive lesions have not been previously investigated, to the best of our knowledge. Within this context, this was the first time that TMP as microparticles and nanoparticles incorporated into NaF varnishes has been assessed using an early enamel erosive model, which allows the effects of the test products to be assessed within each timepoint of erosive challenge. The present study assessed the additional benefit of TMP in 5% NaF, colophony-based varnishes, in which the benefit of conventional (micrometric) TMP was shown to be around 43% compared with 5% NaF (after the last erosive challenge). Such effects were further increased to 60%–67% when nanosized TMP was added to the varnishes.

Although this additional protective effect of nanosized particles over micrometric TMP (30%–40%) cannot be directly extrapolated to *in vivo* conditions, it indicates that such formulations might be a promising alternative for preventing enamel mineral loss upon erosive challenges. In this sense, it is noteworthy that despite all test formulations demonstrating immediate (first challenge) and sustained (second to fourth challenge) protective effects, the TMP-containing varnishes (especially those supplemented with nanosized particles) were more effective in sustaining the protective effects against surface hardness change when compared with 5% NaF. In fact, the percentage of surface hardness change promoted by the 5% NaF/5% TMPnano after the fourth acid challenge (10%) was very similar to that already seen for the 5% NaF after the first challenge (~8%), which seems to be attributed to the greater reactivity of nanosized TMP, owing to the higher ratio of surface area to volume when compared with conventional (micrometric) particles. This aspect is paramount from a clinical perspective, given that vehicles for professional application are used at much lower frequency than products for home use. Furthermore, for enamel erosion, the desirable predominant effect of fluoride-based preventive measures is the formation of an acid-resistant mechanical barrier rather than mineral precipitation. Given that the formation of CaF_2 is significantly reduced for TMP-containing varnishes [28], the enhanced protective effect of these formulations can be regarded as a result of the strong interactions of TMP with tooth enamel, limiting acid diffusion [28].

Despite the trends above, some limitations imposed by the study protocol should be emphasized. Firstly, in order to create highly controlled conditions and isolate the effects of the tested varnishes, the combined effects of the clinically applied modality of fluoride application (i.e., the varnish) have not been tested with the use of a fluoridated dentifrice, which usually occurs under clinical conditions. In this sense, this variable should be added to future protocols, reflecting real-world scenarios. This short-term erosion model provides valuable information on the effects of preventive agents against enamel softening after exposure to acidic challenges, given that surface hardness has been shown to be suitable for analyzing minor changes in surface enamel, without bulk enamel loss [33]. Nonetheless, in order to further investigate the potential application of the TMP-containing varnishes used in the present study, it would be instructive to assess the effect of these formulations in promoting the remineralization of enamel with initial erosion lesions, as well as the effects of this therapy against prolonged erosive challenges. Additionally, it is important to mention that although bovine enamel is commonly employed for similar purposes for its reliability, it is essential to recognize that human teeth may differ from the bovine teeth, presenting some different mineral traits [34–37]. Finally, given the complex interplay among chemical, physical, and behavioral aspects involved in enamel erosive wear, the assessment of the anti-erosive potential of the TMP-containing varnishes under *in situ* conditions, in subjects regularly using fluoridated toothpastes, could provide relevant information related to the real benefit of these varnishes for the clinical practice.

5. Conclusions

Based on the information presented above, it can be concluded that incorporating micrometric TMP into a 5% NaF varnish significantly improved their effect against enamel softening in an initial enamel erosion model *in vitro*. Additionally, the reduction of the TMP particle size to the nanoscale was demonstrated to enhance such effects, as TMPnano-containing F varnishes presented significantly greater effects in comparison to their counterparts containing micrometric TMPs.

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