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Effect of Titanium Tetrafluoride and Sodium Fluoride on Erosion Progression in Enamel and Dentine in vitro

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Key Words
Dentine · Enamel · Erosion · Titanium tetrafluoride

Abstract
Our aim was to investigate the effect of TiF_4 solutions on mineral loss on enamel and dentine in vitro. Samples were fluoridated 1 × 5 min per day with 1.64% w/v TiF_4 or 2.2% w/v NaF solutions, each with a pH of 1.2, and then subjected to a cyclic de- and remineralization procedure for 5 days. Demineralization was performed for 6 × 10 min per day with citric acid (pH 2.3). In controls no fluoridation was performed. Mineral content was determined by longitudinal microradiography. Enamel mineral loss was markedly reduced by both fluoride solutions, but TiF_4 was significantly more effective than NaF: cumulative mineral loss on day 3 was 61.7 ± 15.0 μm in the NaF and 34.2 ± 13.1 μm in the TiF_4 group ($p \leq 0.001$) compared with 121.0 ± 27.0 μm in the control group. Dentine mineral loss ceased after both TiF_4 and NaF applications (cumulative mineral loss on day 5 in controls: 61.0 ± 17.0 μm, in the TiF_4 group: 15.4 ± 13.4 μm and in the NaF group: 21.8 ± 11.8 μm). Both TiF_4 and NaF application reduced mineral loss both on enamel and dentine, which could open new possibilities for a symptomatic therapy of erosions.

Erosion progression can be diminished by application of fluoride preparations, like acidic sodium, stannous or amine fluoride preparations [Attin et al., 1999; Ganss et al., 2001, 2004a]. The principle of its protective effect is the precipitation of CaF_2-like materials on the tooth surface. One major disadvantage of these protective coatings is that they are readily dissolved in acidic solutions. So the efficacy of fluoride in preventing dental hard tissues from erosions is limited, at least in enamel and under in vitro conditions [Ganss et al., 2001]. After TiF_4 application, other precipitates than CaF_2 are formed, which appear as a glaze-like layer [Mundorff et al., 1972; Wei et al., 1976] and are described as hard and hydrophobic [Büyükyilmaz et al., 1997b]. The layer seems to be relatively stable against mechanical and chemical influences [Büyükyilmaz et al., 1997a; Skartveit et al., 1989; Tveit et al., 1983], particularly against strong hydrochloric acid [Büyükyilmaz et al., 1997b]. One assumption is that an interaction between the TiF_4 and the proteins on the tooth surface influences the fluoride uptake from TiF_4 [Gu et al., 1996] and modifies the formation of the glaze [Mundorff et al., 1972]. A different hypothesis is that titanium reacts with oxygen atoms in phosphate groups on the tooth surface, forming stable titanium oxide [Tveit et al., 1988]. Most studies on TiF_4 dealt with its caries-preventive effect. It was found that TiF_4 revealed protection from artificial lesions in vitro [Wefel, 1982; Wefel and Harless, 1982] and a caries-inhibiting potential in rats [Skartveit et al., 1991] and in humans in vivo [Büyükyilmaz et al., 1994, 1997a].

However, only little is known about the efficacy of TiF_4 preparations with respect to dental erosion. Vieira et al. [2005] found in an in vitro study that TiF_4 gels with a concentration of 1% (pH 2.5) or 4% (pH 3.2) could reduce

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erosive mineral loss by about 16% in bovine enamel compared with a non-fluoridated control group. In this study TiF_4 was not more effective than several other fluoride products. However, divers other studies are more promising with regard to the efficacy of TiF_4 in dental erosions. It has been shown that the application of TiF_4 could reduce the enamel solubility in acetic acid buffer by about 95% compared to 25% after 2% NaF treatment [Shrestha et al., 1972]. Recent studies have demonstrated that TiF_4 inhibits enamel softening [Büyükyilmaz et al., 1997b] and prevents erosive tissue loss in bovine enamel induced by multiple acid exposures [van Rijkom et al., 2003]. Its efficacy in preventing erosion in dentine, however, has not yet been investigated.

The present study therefore sought to quantify the effect of TiF_4 and NaF solutions, which were adjusted to the same pH, on erosion progression in human dentine and enamel in vitro exposed to multiple de- and remineralization cycles.

Materials and Methods

Solutions

For fluoride treatment a 1.64% w/v TiF_4 (1% w/v F, pH 1.2, Strem Chemicals Inc., Newburyport, Mass., USA) and a 2.2% w/v NaF solution (1% w/v F, pH 1.2, Merck, Darmstadt, Germany) were used. The NaF solution was adjusted to pH 1.2 with 15.4 g of H_3PO_4 per 100 ml (Merck). A remineralization solution according to Gerrard and Winter [1986] was used. The solution was prepared with 0.4 g H_3PO_4 dissolved in 40 ml distilled water, 1.5 g KCl dissolved in 100 ml distilled water, 1.0 g Na_2CO_3 dissolved in 100 ml distilled water, and 0.2 g $CaCl_2$ (anhydrous) dissolved in 100 ml distilled water (all chemicals from Merck). These solutions were mixed and topped up to make 1 liter with distilled water. Erosive demineralization was performed with citric acid (1%, pH 2.3; anhydrous citric acid, Merck).

Specimen Preparation

The study was performed according to the protocol of Ganss et al. [2001]. Plano-parallel enamel and dentine slices were prepared from freshly extracted, previously impacted human third molars, ground to a thickness of 400 μm (enamel) or 750 μm (dentine), and polished under flowing water (Exakt Abrasive Cutting System and Exakt Microgrinder, Exakt-Apparatebau, Norderstedt, Germany; P800 and P1200 silicon carbide abrasive paper, Leco, St. Joseph, Mo., USA). The enamel surfaces were carefully checked under a microscope (magnification ×10, SMZ-1 Zoom Stereomicroscope, Nikon GmbH, Düsseldorf, Germany) for exposed dentine and the dentine surfaces for remnants of enamel. A total of 75 enamel and 75 dentine specimens were prepared and stored in 100% humidity until use. The samples were mounted on holders for longitudinal microradiography with a light curing acrylate (Technovit 7230 VLC, Kulzer-Exakt, Wehrheim, Germany), leaving the experimental area undisturbed.

Treatments

The specimens were subjected to a cyclic de- and remineralization procedure over 5 days. Dentine and enamel specimens were each randomly divided into 3 groups of 25. Group 1 represented the control: erosive demineralization but no fluoridation was carried out. Additionally to the erosive demineralization, in Group 2 the TiF_4 solution and in Group 3 the NaF solution for fluoride treatment was used. The experimental procedures started at 09.00 h. At the beginning of each experimental day, specimens were treated with fluoride for 1 × 5 min before acidic exposure. The demineralization procedure was performed with citric acid for 6 × 10 min per day. The last demineralization period per day was performed at 16.30 h. Specimens were stored in remineralization solution after demineralization treatments for 1 h except after the last treatment, when they were stored in remineralization solution overnight. After de- and after remineralization specimens were rinsed with tap water for 1 min. To achieve constant immersion times, the specimens were placed on plastic sieves which were transferred to plastic containers filled with 200 ml of demineralization, remineralization or fluoride solution. Solutions were renewed at the beginning of each experimental day. All procedures were carried out under gentle agitation at 37°C.

Tissue Loss Measurements

The mineral content was determined using longitudinal microradiography [de Josselin de Jong et al., 1988]. An X-ray projection of the sample slice together with an aluminium calibration step-wedge was made at baseline and after each experimental day on a high-resolution film (high-speed holographic film, Kodak SO-253, Kodak, Stuttgart, Germany), which was developed under standardized conditions. The mineral content was calculated automatically using a computer-controlled microdensitometer (Leitz MPV compact Ortholux II, Leitz, Wetzlar, Germany). The values were calculated under the assumption that the mineral content was 87 vol% for enamel and 47 vol% for dentine [Nikiforuk, 1985]. The differences between the values at baseline and after each day were converted to tissue loss.

Statistics

The statistical procedures were performed with SPSS 10.0 for Windows. The Kolmogorov-Smirnov test was used to check for normal distribution. For statistical analysis of the mineral status the repeated measures general linear model with univariate multiple comparisons (Tukey's post hoc) and repeated measures general linear model of within-subject contrasts with Bonferroni adjustment were used. For comparison of mineral status at the end of the experiment (enamel day 3, dentine day 5) the independent sample t test was performed. The level of significance was set at 0.05.

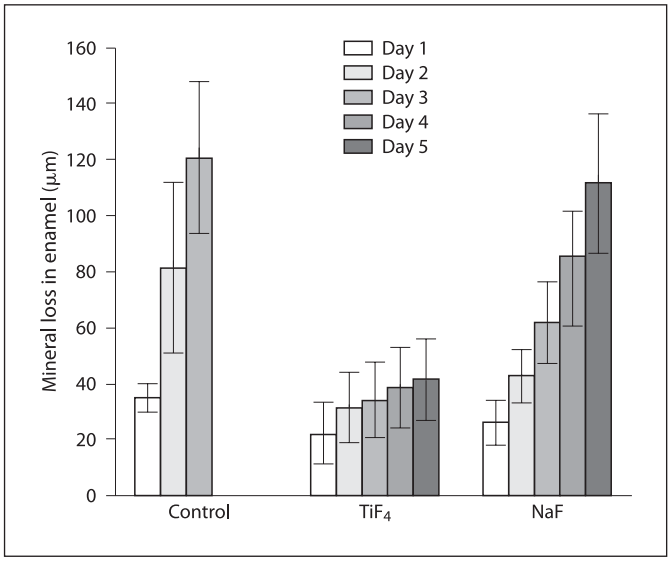
Results

For enamel (fig. 1) mean mineral loss per day was 40.3 ± 6.0 μm in the control group and 22.4 ± 4.2 μm in the NaF group. In both groups, mineral loss increased significantly on each day compared to the day before (for all differences $p \leq 0.001$). In the TiF_4 group mineral loss per day was much lower (8.3 ± 8.1 μm), but the daily

increase was also significant when compared to the day before ($p \leq 0.001$). On day 3, mineral loss was 121.0 ± 27.0 μm in the controls compared to 61.7 ± 15.0 μm after NaF ($p \leq 0.001$) and 34.2 ± 13.1 μm ($p \leq 0.001$) after TiF_4 fluoridation. In comparison to the controls, a reduction of mineral loss of 49.0% after NaF and 71.7% after TiF_4 application was seen after 3 days. The overall effect for all experimental days of fluoride treatment was significantly greater for the TiF_4 and NaF groups than for the controls ($p \leq 0.001$); the overall effect of TiF_4 exceeded that of NaF ($p \leq 0.01$).

Since the mineral loss in the control group was large and amounted to one third of the thickness of the sample, the experiment was stopped at this time point for the control group. In the NaF group mineral loss on day 5 was 111.8 ± 25.1 μm and in the TiF_4 group 41.7 ± 14.4 μm.

For dentine specimens (fig. 2) mean mineral loss per day was 12.2 ± 5.7 μm in the control group, 4.4 ± 1.1 μm in the NaF group and 2.9 ± 2.9 μm in the TiF_4 group. In the control group, the daily increase of mineral loss was significant when compared to the day before (day 1–4: $p \leq 0.001$, last day: $p \leq 0.05$). In the NaF group the loss also increased significantly ($p \leq 0.01$) from day to day, except from day 2 to day 3 (n.s.), whereas in the TiF_4 group the mineral loss significantly increased from day 1 to day 2 ($p \leq 0.001$) and stagnated the following (all differences n.s.). After day 5 a tendency to mineral gain could be seen (n.s.). For all experimental days, the mineral loss in the control group was significantly higher than in both fluoride treatment groups. Mean mineral loss after 5 days was 61.0 ± 17.0 μm in the control group, 21.8 ± 11.8 μm in the NaF group ($p \leq 0.001$ compared to the control group) and 15.4 ± 13.4 μm in the TiF_4 group ($p \leq 0.001$ compared to the control group; n.s. compared to the NaF group). In comparison to the control group the mean overall reduction of mineral loss was 64.3% in the NaF group and 74.8% in the TiF_4 group. The overall effect of all experimental days of TiF_4 and NaF was significantly greater than for the controls (TiF_4 vs. control and NaF vs. control: $p \leq 0.001$); the overall effect of TiF_4 was similar to NaF (n.s.).



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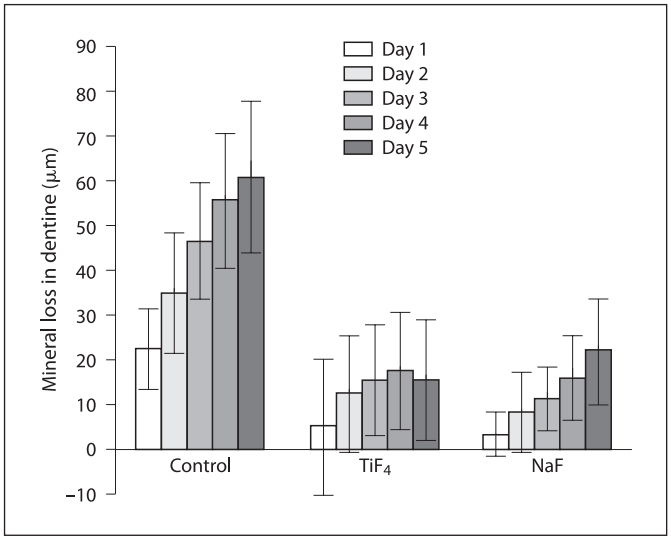

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Fig. 1. Erosive mineral loss (mean ± SD) in enamel after 5 days of cyclic de- and remineralization procedure.
Fig. 2. Erosive mineral loss (mean ± SD) in dentine after 5 days of cyclic de- and remineralization procedure.

Discussion

Information about the efficacy of fluoride preparations on erosion progression without abrasive influences is limited. Hughes et al. [2004] found that, in vitro, fluoride pretreatment led to a reduction of enamel erosion by acidic beverages: by about 10% after a neutral fluoride preparation and about 24% after acidulated fluoride gel. Van Rijkom et al. [2003] found that enamel erosion was reduced about 20% by a NaF gel compared to untreated controls. Similar effects were shown for commercially available acidic fluoride preparations [Ganss et al., 2001]. In dentine, fluoride applications were much more effective, but it appears that high amounts of fluoride are necessary, thus requiring multiple applications. An intensive fluoridation measure using frequent rinsing and gel applications, however, is cumbersome and expensive for patients. Hence, a

better modification of dental surfaces than resulting from NaF or amine fluoride treatment is desirable.

A symptomatic therapy with intensive fluoridation is particularly relevant for risk groups, e.g. vegetarians but also patients with eating disorders, where the frequency of acid attacks can be high: in subjects living on a raw food diet, a median frequency of acidic food consumption of 4.8 intakes per day (maximum 16.1) was found [Ganss et al., 1999]. Usually the pH of the oral fluids after an acid intake returns to neutral values after 1–3 min [Imfeld, 1983; Meurman et al., 1987], but in some cases it takes up to 10 min for the pH to rise to 4.0 or above [Imfeld, 1983]. Hence the experimental setting with 6 × 10 min demineralization per day was selected. The pH (2.3) of the demineralization solution we used was comparable to beverages with high erosive potential [Seow and Thong, 2005; Lussi et al., 1995]. Furthermore, the erosive procedures were the same as in our previously performed studies, which assures comparability to the other results.

Particularly after application of TiF_4, but also when the pH-adjusted NaF solution was used, the reduction of mineral loss in enamel (49.0% after NaF, 71.7% after TiF_4 application compared to controls on day 3) was much higher than in the previous in vitro experiment [Ganss et al., 2001], even though only 1 application per day was used. A major difference between the fluoride preparations of these studies was in the pH, which was much lower in the present study (1.2 compared to 4.2). It can be suggested that the pH plays a decisive role for the efficacy in reducing mineral loss. This emphasizes the need for pH adjustment in studies comparing the efficacy of fluoride preparations but particularly the need for very acidic fluoride preparations in the therapy of erosions. This hypothesis is supported by the study of Saxegaard and Rølla [1988]. They found that acidulated fluoride preparations led to high precipitation of fluoride compounds (CaF_2-like layer) on enamel surfaces. The CaF_2-like layer acts as a protective coating that has to be dissolved during an acid attack before the dental hard tissue beneath is affected. The higher the fluoride concentration and the lower the pH of a fluoride preparation, the thicker the CaF_2-like layer will become [Saxegaard and Rølla, 1988] without producing erosions as a result of the low pH of the fluoride preparation [Lussi and Jaeggi, 2001]. Therefore the pH level may play an important role in the efficacy of some fluoride preparations as dental erosion therapy. It must, however, also be considered that adding phosphoric acid to the NaF solution not only changes pH but adds phosphate and this might influence the effectiveness more than if, for instance, hydrochloric acid had been used.

Independent from the pH, TiF_4 inhibited mineral loss in enamel considerably better than the pH-adjusted NaF, which confirms results of van Rijkom et al. [2003]. They found that calcium loss and depth of erosive lesions decreased after treatment with a 4% TiF_4 solution (pH 1.5) by 40% compared with treatment with a neutral 1% NaF gel (20%). With regard to the above-mentioned considerations, however, the efficacy of the NaF preparation could be higher, if the same pH (1.5) in both solutions had been used.

A similar study to the present one was performed by Vieira et al. [2005], who investigated the influence of 1 and 4% TiF_4 gel, 1 and 0.25% AmF solution on calcium loss and erosion depth. Their main result was that they could not find a significant difference between the controls and the fluoride groups, or between the fluoride groups. In the present study we also found no significant differences between the fluoride groups after the first experimental day (demineralization time of 60 min). But in contrast to their investigations we found a statistically significant difference between the fluoride groups and the controls. Possibly TiF_4 took effect only after prolonged experimental periods or after repeated applications. But the differences could also depend on the formula or again on the pH of the TiF_4 preparation.

The protecting effect of TiF_4 has been attributed to the formation of a glaze-like surface layer. Even though there is evidence that the glaze is stable against strong acids [Büyükyilmaz et al., 1997b; Wefel and Harless, 1981], the reaction mechanisms of TiF_4 with the tooth surfaces and therefore the reason for the stability of the glaze and the protective effect are not definitely clarified. But it can be suggested that the titanium ion plays a decisive role. Titanium ions can bind to, and penetrate, sound or decayed enamel surfaces [Chevitarese et al., 2004; Clarkson and Wefel, 1979], but there is no information about the retention of titanium under acidic conditions. We have observed, in agreement with these findings, that high amounts of titanium could be detected directly after fluoridation and nearly half survived repeated erosive demineralization procedures at least in enamel [4.4 ± 1.0 wt% directly after fluoridation, 1.9 ± 0.9 wt% ($p \leq 0.01$) after 6, and 1.7 ± 1.1 wt% ($p \leq 0.01$) after 18 demineralization procedures; data not shown]. The long-lasting retention of titanium on the surface suggests that it would be worth investigating whether a lower application frequency per week would be sufficient to inhibit erosion progression. Further studies for dose-finding, using TiF_4 solutions with lower concentrations or higher pH, should be performed to give more information.

For dentine, the present study confirmed the great efficacy of fluoride on erosion progression [Ganss et al., 2001, 2004b]. Mineral loss was significantly reduced and progression stagnated, after both NaF and TiF_4 application. The differences in mineral loss after NaF or TiF_4 treatment were not significant, which was interesting, since neither pH nor the fluoride compound appeared to be relevant factors. This is probably due to an increasing thickness of demineralized organic dentine matrix at the surface with continuing demineralization. There is evidence that this layer is essential for the efficacy of fluoride applications [Ganss et al., 2004b], which emphasizes the need for stabilization of these protecting layers. Perhaps, in the case of TiF_4, the titanium ion might play an essential role because of its protein-binding properties [Gu et al., 1996; Mundorff et al., 1972].

In conclusion, the considerable reduction of mineral loss could open new perspectives for a symptomatic therapy of erosions. The particular advantage of TiF_4 preparations is that they are likewise effective on both enamel and dentine. Especially patients in risk groups, for e.g. vegetarians and as well persons with eating disorders, who are exposed to frequent extrinsic or intrinsic acids and often suffer from severe and rapidly progressing dental tissue loss, could benefit from a respective new therapeutic approach.

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