The protective effect of topical fluoride treatments in dentine lesions

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Chapter 7

General Discussion
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In the field of Cariology, the management of dental caries has been shifted from the restorative approach to the non- to minimally invasive approach since dental caries is considered being a disease rather than a cavity [Gao et al., 2016]. Therefore, an approach that focuses on treating the disease rather than the symptoms was highly needed, and so the non-restorative cavity control (NRCC) approach was developed to treat dentine cavities of the primary dentition and coronal smooth surfaces lesions or root caries of the permanent dentition [Nygad and Fejerskov, 1986; Fejerskov and Nyvad, 2017; van Strijp and van Loveren, 2018]. In this approach, the main effort is not to restore the dentine cavity, but to provide a proper environment for the cavitated dentine lesions to rebuild the partially demineralized mineral. This proper environment works on two aspects; chemical changes of the dentine lesions, including inhibition of demineralization and enhancement of remineralization, and microbiological control that will be achieved by plaque removal. The results of these two aspects are observed clinically as caries arrestment, which indicates the success of the NRCC approach. In this approach, the patient, parents or caregivers are targeted to be part of the treatment plan. This gives them more responsibility to maintain the oral hygiene and to change dental health behavior towards more dental home care and less sugar intake. Different protocols of NRCC have been applied to cavitated dentine lesions in pediatric and geriatric populations [Nygad and Fejerskov, 1986; Schwarz et al., 1996; Mijan et al., 2014]. Some observational studies of NRCC encouraged the brushing of open cavities using fluoridated toothpaste [Schwarz et al., 1996; Lo et al., 1998]. Others combined tooth brushing with slicing and opening of the cavities and subsequently application of topically fluoride products [Peretz and Gluck, 2006]. These observational studies showed that the combination of the three methods (tooth brushing, opening of the cavities, and application of topical fluoride) revealed a significant caries arrestment. It was expected that the topical fluoride products played a significant role in enhancing dentine caries arrestment as a result of NRCC. However, the effect of the topical fluoride products on the chemical (de- and remineralization), histological (mineral content and distribution within the lesion), and microbiological aspects of dentine caries arrestment were rarely studied. For this reason, the current thesis aimed to emphasize the chemical and histological efficacy of the different topically applied fluoride products on dentine lesions. This information will contribute to answering the question, “Which topically applied fluoride product is the most effective in dentine caries management?”. The overall results of the conducted experiments are discussed critically in this chapter, including suggestions for future studies in the field of Cariology.
Dentine lesions and topically applied fluoride products

The effect of fluoride on demineralized dentine lesions during de- and remineralization was the topic of interest in the current thesis. The outcome measurements focused on the chemical and histological (mineral content and distribution) aspects of dentine lesions after application of topical fluoride products and subsequent de- and remineralization. To understand the process of caries arrestment in the NRCC approach, the current experiments used demineralized dentine lesions to investigate the chemical and histological features of the interaction between the topical fluoride products and the dentine tissue. This step is essential in translating the clinical condition of dentine caries to more controlled-in vitro condition which helps in explaining the process of caries arrestment or even dentine remineralization more closely.

In the current experiments, variation in the baseline lesions (initial lesions) was observed, which thought to influence the final results of each experiment. However, it is not clear why the baseline lesions differed between the experiments, while the same preparation methods were followed. This could be attributed to different factors, including not only the differences between bovine teeth but also within one tooth. The stage of tooth maturation might cause variations in the final results. In addition to this reason, we expected some technical matters in tooth preparation that we could not avoid, for instance, the anatomical differences when the dentine specimens were prepared from the middle third or cervical third of the tooth, as well as, the location and distribution of the dentine specimens within the tray during artificial caries formation. All these unavoidable factors in the experimental conditions might affect the final results, and thus transversal microradiography (TMR) is an important outcome to show the differences in the baseline lesions and how these differences will influence the interaction between the fluoride products and the dentine lesions.

In Chapter 2 the main focus was to study the interaction between dentine lesions and topically applied fluoride products under a constant remineralization condition. This was to investigate the histological interaction between the dentine lesions and the different fluoride products (SDF, NaF, TiF₄, and SnF₂). Interestingly, all experimental groups showed remineralization, including the control group, regardless of the presence or absence of fluoride. This outcome was not expected since the topically applied fluorides were different in formulas and concentrations. This indicates that the experiment in Chapter 2 was more influenced by the mineral of the baseline lesions and the constant remineralization than the different fluoride products. The subsequent experiments in Chapter 3 and 4 were designed to alternate the conditions between de- and remineralization in a pH-cycling model. The combination of de- and remineralization in this model was to simulate the dynamics of mineral loss and gain in the caries process [White, 1995]. The results of this model disclosed
differences in the amount of de- and remineralization when the same fluoride products used in Chapter 2 were applied to dentine lesions. Significant inhibition of the net demineralization (combined data of calcium loss and uptake in de- and remineralization cycles) was observed in all fluoride groups compared to the non treatment group (Chapter 3). Remarkably, demineralization was observed in SnF$_2$ and no treatment groups during remineralization phase. We speculate that the alternating process between de- and remineralization in the pH-cycling might not be adequate for the rinsing step to rinse out or neutralize the acid. Additional reasons, it could be due to inability of the remineralization solution to neutralize the remaining acid in the dentine pores, or because of the continues leaking of calcium from the dentine lesions even in the remineralization cycle, which could be not even sufficient for the low fluoride concentration of SnF$_2$ (1,000 ppm F) to enhance mineral gain. For this reason, the pH-cycling conditions in Chapter 5 and 6 were modified from pH 4.8 and pH 7.1 in de- and remineralization cycles, respectively, to pH 5.0 and pH 7.2 in both de- and remineralization cycles, respectively, while calcium and phosphate values remained the same. The chemical data of Chapter 5 showed significant remineralization in all experimental groups including the no treatment group (control) in the remineralization phase. This finding indicated that the reactivity between the topical fluoride products and the dentine lesions is influenced by the experimental condition of de- and remineralization processes and the pH of the buffers. This points out the importance of understanding how the interaction between dentine lesions and fluoride products would proceed under different oral conditions when the salivary pH changes throughout the day.

In the current experiments, a single fluoride application has been chosen over multiple applications. This was to mimic the clinical usage in which the dental care professional performs fluoride application once in three to six months. The findings in Chapter 3, 4, 5, and 6 revealed constant effectiveness reflected in the chemical data of the applied fluorides, which last for the whole period of the experiment. Regardless of the differences in the fluoride products in Chapter 3 and 4, all products could inhibit dentine demineralization or enhance dentine remineralization significantly higher than no treatment group after single application. This finding included not only the products with high fluoride concentrations like SDF and NaF, but also SnF$_2$ of low fluoride concentration (1,000 ppm F). These results indicated that a single application is sufficient to inhibit demineralization and enhance remineralization of the dentine lesion over time, and so highly support the application of topical fluoride products to the cavitated dentine lesions in the NRCC approach.

This thesis has chosen different fluoride products (as shown in Chapter 2, 3, and 4), with different formulas and concentrations. For example, NaF varnish has been chosen in the current experiments because it is the most commonly used product by dental care professionals in preventing the progression of dental caries [Petersson et al., 2004; Chu
and Lo, 2006]. However, the efficacy of sodium fluoride (NaF) varnish in dentine caries management is not fully known yet. Numerous studies have compared the efficacy of NaF to silver diamine fluoride (SDF) on dentine lesions [Chu et al., 2002; Duangthip et al., 2015; Duangthip et al., 2018; Wierichs et al., 2018]. These studies showed a superior effect in SDF treated lesions compared to NaF. It has been claimed that SDF is very effective not only because of the presence of the fluoride component but also because of the metal component of silver [Yamaga et al., 1972; Peng et al., 2012]. It was suggested that SDF possesses two activities in dentine caries management; anti-demineralizing and anti-microbial activities [Hu et al., 2018]. It is, however, unclear whether silver could participate in the anti-demineralizing activity besides the fluoride component in the SDF. The same pertains to the metal fluorides, titanium tetrafluoride (TiF$_4$) and stannous fluoride (SnF$_2$) were included in Chapter 2, 3, and 4. In Chapter 5 and 6 we chose to compare SDF to potassium fluoride (KF) instead of NaF. Due to the solubility of NaF salt in water (at room temperature; 40.4 g/L), it was not possible to reach the same fluoride concentration of 44,800 ppm F to be able to compare between SDF and NaF. The solubility of KF is much higher than NaF, which makes that comparison possible.

As a result of the different formulas and concentrations of the products used in this thesis, we expected to find differences in their effect on dentine lesions. However, the results in Chapter 2 showed the same amount of remineralization among the fluoride products and the no treatment group (control). We speculate that this might be due to different factors that affect the reaction of fluoride in the dentine lesion, which is perhaps attributed to the dentine large surface area [Kawasaki et al., 2000], dilution of fluoride in the large volume of the remineralization buffer, and the presence of the mineral growth inhibitor in the metal fluoride (SDF, TiF$_4$, and SnF$_2$) [Lippert, 2016]. All those factors could reduce the reactivity of the fluoride product under the constant remineralization condition. For this reason, the condition has been changed in Chapter 3, 4, 5, and 6, and a pH-cycling model has been chosen to mimic the oral cavity processes of de- and remineralization. This model revealed differences in the reactivity of the fluoride products with dentine lesions. It was expected to find a significant inhibition of demineralization and/or enhancement of remineralization in the higher fluoride concentration products, such as SDF and NaF. SDF showed significant efficacy in inhibiting demineralization and enhancing remineralization in the de- and remineralization phases of the pH-cycling, respectively. Differently, NaF disclosed an effective inhibition of demineralization and enhancement of remineralization but was not significantly better than TiF$_4$, which had a lower fluoride concentration than NaF. Regardless of the differences in efficacy of the applied fluoride products, all these products were sufficient to repair the dentine lesions, including the low concentration of SnF$_2$ (1,000 ppm F). A constant effect of fluoride products was observed throughout the
whole period of the experiment. These findings indicated that the application of fluoride (high or low concentration) is effective in dentine caries management, and it will add extra benefits to the NRCC approach.

The superior effect of SDF in Chapter 3 and 4 points out the importance of understanding the chemical interaction between SDF and dentine lesions more closely. As well as, the histological appearance of the mineral deposition throughout the layers of dentine lesions after a single application of SDF. In Chapters 3 and 4, we assumed that the superior effect of SDF is perhaps attributed to two factors; either the high fluoride concentration of the product or the presence of the non-fluoride component (silver). For this reason, the experiment in Chapter 5 and 6 was designed to focus on the high fluoride concentration of SDF and to determine whether silver play a major role in the anti-demineralizing effect of the SDF product. Therefore, another fluoride product with the same fluoride concentration as SDF was developed. Thus, three fluoride concentrations; 4.1%, 1.025%, 0.26% of either SDF or KF were applied once to demineralized dentine lesions and then pH-cycled. The chemical and histological data of this experiment revealed no superior effect of SDF over KF under the chosen conditions. This finding indicated that the significant effect of SDF in Chapter 3 and 4 is due to its high fluoride concentration mainly, whereas the presence of silver in the product did not significantly contribute to the processes of inhibiting dentine demineralization and enhancing dentine remineralization. Take into account that this thesis did not address the microbiological aspects of topical fluorides, and specifically SDF, in dentine caries management. In vitro studies have been shown that 38% SDF was effective against bacterial species, such as Streptococcus mutans, S. sobrinus, Lactobacillus acidophilus, L. rhamnosus, and Actinomyces naeslundii [Mei et al., 2013; Lou et al., 2018]. However, recent studies revealed no significant changes in the microbial composition of the biofilm covering the dentine lesion before and after the application of SDF [Milgrom et al., 2018; Mitwalli et al., 2019]. Therefore, further studies are recommended to examine the microbiological aspect of the different fluoride products, and particularly the role of SDF.

In the current thesis, the microradiography of the dentine lesions treated with SDF showed a unique pattern of mineral deposition. In Chapter 2, the mineral was deposited mainly on the surface of the dentine lesion, whereas in Chapter 4, a high peak of mineral deposition was observed in the body of the dentine lesion. The differences in these findings are probably attributed to the differences in the experimental conditions between Chapter 2 and 4. However, it was suggested that silver in SDF could influence the final results in the microradiographic images, because of the high radiopacity of the silver deposits. Therefore, to exclude the role of silver in the radiopacity of the microradiographic images, we decided to conduct an additional experiment using energy dispersive X-ray (EDS) to analyze the elemental composition of the high peak of mineral deposition in Chapter 4. That experiment
revealed that the alternating process of de- and remineralization in the pH-cycling model had redistributed silver from the surface to the deeper layers inside the dentine lesion. For this reason, the peak has been found in the body of the pH-cycled dentine lesions, and not in the constantly remineralized lesion of Chapter 2. The EDS analysis of this peak disclosed a combination of calcium, phosphate, and silver. This finding is in line with a previous study that found calcium, phosphate, and silver, and considered these components as essential elements in the dentine lesions treated by SDF [Li et al., 2019].

In Chapter 4 the intersection points (IP) between the profiles of the baseline lesion and the experimental groups (SDF, NaF, TiF₄, SnF₂, and control) had divided the lesions into the outer part (zone 1) and deeper part (zone 2). The method of using the intersection point in this chapter was essential to determine the amount of mineral loss and gain throughout the lesion depth. SDF showed a high peak of mineral deposition in zone 1, and less demineralization (secondary lesion) was observed in zone 2 compared to the other groups. However, the high peak of mineral deposition and the development of the secondary lesion that was observed in Chapter 4 were missing in the experiment described in Chapter 6. For this reason, the method of the intersection point was not used in Chapter 6. The absence of the high peak of mineral deposition and secondary lesion in Chapter 6 could be related to different factors, including the slight changes in the experimental conditions and the pH of the de- and remineralization buffers. In addition, change in the SDF brand between the experiment in Chapter 2 and 4 (30% SDF; 35,400 ppm F; Ancarie Cariostatico solution; Maquira; Brazil) and the experiment in Chapter 5 and 6 (38% SDF: 41,000 ppm F; ARGENATE, VladMiVa, Russia) might play a role in the differences of the mineral content profiles between these experiments.

**Conclusions**

This thesis aimed to compare the effect of various topically applied fluoride products on demineralized dentine lesions. The chemical and histological aspects of demineralized dentine lesions after the application of topical fluoride products were examined. This would help to understand the arrestment of demineralized dentine lesions by topically applied fluoride in the NRCC approach. This thesis also aimed at finding the most effective topically applied fluoride product in dentine caries management. The following conclusions can be drawn from the results of this thesis:

The vulnerability of the dentine tissue/lesions is highly influenced by experimental conditions. Differences in the baseline (initial) lesions among the current experiments, and changes in the condition from remineralization only to alternating de- and remineralization
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(pH-cycling model) revealed differences in the interaction between the topically applied fluoride products and the dentine lesions, and thus differences in the effectiveness of inhibiting demineralization and enhancing remineralization. Apparently, fluoride products are effective when the experimental conditions simulate the oral cavity to some extent.

The applications of topical fluoride products (SDF, NaF, TiF₄, and SnF₂) were, although differently, effective in inhibiting demineralization and enhancing remineralization of the dentine lesions. Regardless of the differences in formulas and concentrations, all products showed a constant efficacy during the experiment.

Application of SDF to demineralized dentine showed a superior effect over the other topically applied fluoride products (NaF, TiF₄, and SnF₂). SDF showed significant inhibition of mineral loss, as well as enhancement of mineral gain throughout the depth of the dentine lesion. NaF varnish could also repair the dentine lesion to some extent, however, its efficacy was not superior to SDF or even TiF₄. Thus, SDF performed better in dentine caries management than the other fluoride products in the current experiments.

Comparing SDF to another fluoride treatment that has the same fluoride concentration as SDF showed no difference in the effectiveness of these treatments on dentine lesions. This finding revealed that the superior effect of SDF was mainly attributed to its high fluoride concentration being the highest among all topically applied fluoride products in the dental office. The metal ion (silver) in SDF played no role in the anti-demineralizing activity of the product. The anti-microbial activity of SDF has not been addressed in the current thesis.

**Recommendations**

- The application of topical fluoride products to cavitated dentine lesions is recommended to support the success of the NRCC approach.
- SDF is an effective product in dentine caries management and recommended to be used in NRCC.
- More clinical studies are needed to support the microbial aspects of SDF.
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References


