Remineralization Effect of Silver Diamine Fluoride on Artificial Incipient Caries In Primary Teeth

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Abstract

To investigate the remineralization effect of 38% silver diamine fluoride (SDF) on the artificial incipient carious lesion in primary teeth by analyzing mineral density and remineralization percentage of the lesions. Eighteen sound primary incisors were selected to create artificial carious lesions and scanned using Micro Computed tomography scanner (Micro CT) to determine the baseline mineral density of the initial lesions. The samples were randomly allocated into 2 groups [A: deionized water, B: SDF; n=9]. Nine teeth in group B were applied with SDF, while the other group was the control. After that, all samples in both groups were undergoing in pH-cycling process for 7 days and mineral density was re-evaluated and analyzed. The pre and post-treatment mineral densities were used to calculate the remineralization percentage of both groups. A dependent t-test in parametric statistics was used to compare mineral density between pre and post-test within the SDF group. Wilcoxon Signed Ranks test was used to compare mineral density between the pre and post-test within the control group. The percentages of remineralization of both groups were compared using the Mann-Whitney test. Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) with a significance level set at 0.05. The post-test of mean mineral density in the SDF group was significantly higher than the pre-test. However, there was no significance between the pre and post-mineral density in the control group. Furthermore, the mean percentage of remineralization of SDF was significantly higher than the control group. The reason supported the higher remineralization effect of SDF on incipient carious lesion are the mechanism of action and high concentration of fluoride. The SDF can be effectively used to enhance the remineralization and inhibit the demineralization in initial carious lesions of primary teeth.

Keywords: *Demineralization, Mineral density, Remineralization, Silver Diamine Fluoride*

1. Introduction

Dental caries is one of the most common diseases of childhood that can develop as early as the primary teeth begin to erupt. Many risk factors are significantly related to dental caries such as level of cariogenic bacteria groups, dietary habits, frequency of consuming sugar-containing snacks and beverages, and host (Sutthavong et al., 2010).

According to the 8th of Thailand National Oral Health Survey, the percentages of carious lesions were 52.9 in 3-year-old children, 75.6 in 5-year-old children, and 52.0 in 12-year-old children. The percentages of initial carious lesions were 31.1 in 3-year-old children and 31.3 in 5-year-old children. This report evidence indicates that dental caries is still the major concern health issue in Thailand.

Dental caries is a dynamic process. After prolonged exposure to an acid condition, partial dissolution of hydroxyapatite crystals on the enamel will occur. Acid was produced by bacteria in dental plaque, which ferment sugar from beverages and foods in the oral cavity. The demineralization process starts when the dental plaque fluid pH drops to lower or equal to 5.5 (Hicks et al., 2004) and remineralization occurs to neutralize the oral environment to the resting stage, which is the condition pH 7. The failure to remove dental plaque and a highly consume carbohydrate diet will interrupt the equilibrium between demineralization and remineralization process. Then it tipped toward demineralization that may be detectable as white spot lesions, which is considered the initial carious lesion (Featherstone, 2008).

Treatment of dental caries in small children may require advanced clinical skills and sometimes needs local or general anesthesia. Management of the developing carious lesion may involve removal of caries and placement of a restoration. Early detection and management of initial carious lesions can decrease the chances for aggressive restorative dental treatment (Chu, 2000).

In preventive dentistry protocol, fluoride is known to be highly effective to fight against caries. It plays a role of action in the remineralization process. When fluoride is presented in oral fluids, fluorapatite is formed during the remineralization process. Fluorapatite is less soluble than hydroxyapatite under acidic conditions. It is also more resistant to subsequent demineralization when acid is challenged (Cury & Tenuta, 2008). Fluoride has been effectively used in the non-invasive treatment of initial lesions to control dental caries.

The current concept in the management of an incipient carious lesion is to remineralize the lesion by using fluoride or other remineralizing agents. Topical fluoride in various forms has been proven to be effective in dental caries prevention (American Academy of Pediatric Dentistry, 2018a). An application of fluoride can be both home-use or professional-use. Topical self-applied fluoride includes brushing with an appropriate amount of 1000 ppm fluoride toothpaste, which aims to remove plaque biofilm on the tooth surface, fluoride rinse, and fluoride gel. The topical professionally-applied fluoride is namely fluoride gel, fluoride varnish, and silver diamine fluoride (SDF) (AAPD, 2018c).

Among the various professionally applied topical fluorides, the use of silver diamine fluoride (SDF) is currently gaining more popularity due to the favorable results in arresting caries in primary teeth (Duangthip et al., 2017). The mechanism of SDF can be related to bacterial properties on cariogenic biofilm such as *Streptococcus mutans* or *Lactobacillus acidophilus*, which are the important pathogens associated with the initiation and progression of caries. SDF has 2 major components; silver ion and fluoride ion. Silver ion has an intense antibacterial effect on cariogenic biofilm (Chu et al, 2012) and an inhibitory effect on the enzyme that can destroy the collagen. Fluoride ion can increase the mineral density of enamel and microhardness of dentin through remineralization. Although SDF can efficiently prevent carious lesions, it has a major esthetics concern as it can leave dark stains on the tooth surface (Chu & Lo, 2008), which can be misdiagnosed by the clinician as carious lesions (Zhao et al., 2016).

In the previous study considering the demineralization inhibitory effect, 38% SDF has a significantly higher inhibitory effect on dentin demineralization and collagen degradation than 10% NaF (May and Mei et al., 2013). A 30-month clinical study that compared the effectiveness of SDF and NaF varnish in arresting dentin caries among Chinese children found that children who received an annual application of SDF had more arrested caries lesions on primary upper incisors (Chu et al., 2002).

Currently, SDF is effectively used in active cavitated dentine carious lesions with no clinical signs of pulp involvement (AAPD, 2018). However, the study about their effect of remineralization in initial caries on a smooth surface of primary dentition is still unclear. The purpose of this in vitro study is to evaluate the remineralization effect of silver diamine fluoride in arresting initial smooth caries in primary teeth.

2. Objectives

1) To evaluate changes in mineral density on an artificial incipient caries of primary teeth enamel after applying silver diamine fluoride.

2) To compare remineralization effects between applying silver diamine fluoride (SDF) and the control group.

3. Materials and Methods

3.1. Study population

The extracted or naturally exfoliated caries-free primary incisors were selected with the exclusion criteria of the presence of staining, decalcification or white spot lesion, decay, fluorosis, tetracycline staining, enamel defects or enamel hypoplasia, restorations, and crack.

Sample size calculation

The sample size for One-way analysis of variance (ANOVA) was calculated by using G*Power Program version 3.1.9.2. The calculation is included the value of effect size conventions= 0.5311588 from pilot study, α error = 0.05, power (1- β error prob) = 0.7, and number of groups=2. The result is 19 samples. The authors selected 18 samples and equally separated them into 2 groups for this experimental study.

3.2. Materials and methods

Sample collection

18 Sound extracted or naturally exfoliated human primary incisors were stored in 0.1% Thymol solution at room temperature. All teeth were cleaned of soft tissue debris, inspected for cracks, enamel hypoplasia, dental fluorosis, decay, or tetracycline lesion, polished with a fine pumice to remove organic contaminant then kept in normal saline until will be used (Figure 1).

Demineralizing and remineralizing solution preparation

Two demineralizing solutions (D1, D2) and one remineralization solution (R) were prepared.

-D1 consisted of 2.2 mM $CaCl_2$, 2.2 mM NaH_2PO_4, 0.05 M acetic acid, and the pH was adjusted to 4.4 using 1M KOH.

-D2 consisted of the same components as D1, but the pH was adjusted to 4.7 using 1M KOH.

-R consisted of 1.5 mM $CaCl_2$, 0.9 mM NaH_2PO_4, and 0.15 M KCl, and the pH was adjusted to 7.0 with 1 M KOH.

D1 solution was used for the subsurface enamel demineralization test (Figure 1). The D2 and R solutions were used to simulate the supersaturation of apatite minerals found in saliva. Demineralizing and remineralizing solutions were freshly prepared for each cycle, measured pH by using litmus paper, and were kept in separate plastic containers.

The experimental process aims to replicate the pH changes occurring in the oral environment for 7 days. The solutions were replenished with a fresh solution every day. The 38%SDF was applied on day 1 before the start of the pH-cycling process. The detail of the pH-cycling process are shown in Table 1 (Thaveesangpanich et al., 2005).

Table 1 pH cycling process

Period	Procedures
3 hours	Immersed in demineralizing solution (D2) 36 ml
	Rinsed with deionized water 50 ml
	Dried with tissue paper
2 hours	Immersed in remineralizing solution (R) 36 ml
	Rinsed with deionized water 50 ml
	Dried with tissue paper
3 hours	Immersed in demineralizing solution (D2) 36 ml
	Rinsed with deionized water 50 ml
	Dried with tissue paper
overnight	Immersed in remineralizing solution (R) 36 ml
(16 hours at 37 C in controlled environment shaker,	Rinsed with deionized water 50 ml
150 rpm)	Dried with tissue paper

Method flowchart

18 teeth of primary incisors were stored in 0.1% Thymol solution at room temperature

↓

Polished with pumice and kept in normal saline solution until being used

↓

Rinsed with deionized water and wiped off with tissue paper

↓

The specimens' surface were coated with nail varnish, followed by top coated, except for a targeted area of 1 × 1 mm window on each specimen.

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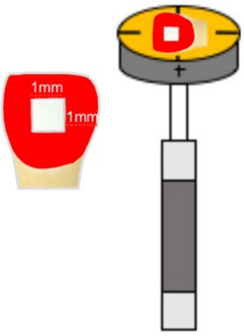

Immersed in 3 ml of the demineralizing solution (D1) and incubated at 37 degrees Celsius for 120 hours to produce artificial demineralizing lesions depth 60 µm

↓

Each specimen was individually fixed in utility wax and putty. The four reference lines of each specimen were created on the putty surface for fixing the position of the specimen in the center and positioning targeted window in perpendicularly.

↓

Measured pre-treatment baseline mineral density by Micro-CT

↓

Divided into 2 groups

↓

Group A: Control group (deionized water)

↓

Immersed in distilled water or deionized water

Group B: 38% SDF group

↓

Rinsed with deionized water

↓

7 days in pH cycling process

↓

Measured post treatment mineral density by Micro-CT

Figure 1 Flow chart method

Mineral density measurement

After pH-cycling for 7 days, the specimens were single-blindly masked before measurement to avoid bias. The mineral density of the 1 × 1 mm^2 window of each specimen was measured using a Micro CT system (Skyscan, Kontich, Belgium). The specimens were scanned at 70 kVp and 114 µA and an isometric voxel size of 9.86 µm. The rotation step is 0.400 deg. The samples were scanned at a standard resolution (1024×1024 pixels). A 1 mm aluminum filter was used to reduce beam hardening. The scanned results were reconstructed and analyzed with Skyscan 1173 Micro CT software version 1.6. The axis of the polished tooth was set parallel to the base of the holder. The reference point of the depth axis (0 µm) was set at the axial position of the sound enamel surface. For bone mineral density (BMD) calibration, mineral reference phantoms 0.25 and 0.75 g /cm^3 were scanned.

The mineral density of each specimen (gHA/cm^3) was determined by volumetric measurements, and the greyscale value was calculated from the Micro CT scan images. The mineral density values were calculated from each specimen every 10 µm through the entire lesion depth. To calculate the lesion depth and mineral gain, a mineral density profile was created by plotting mean mineral density against lesion depth. The remineralization was calculated by subtracting the pre-treatment area under the curve (AUC) from the post-treatment AUC and divided by the pre-treatment area under the curve (AUC) of each group. All values were adjusted to be a percentage. The lesion depth was marked at the depth where the mineral density was equivalent to 95% of the maximum density. The percentage of remineralization (% Remineralization) indicated the proportion of the MD gain and the mineral density of the original lesion, which can be obtained from the equation:

$$\% \text{ Remineralization} = [(\text{AUCpost} - \text{AUCpre})/\text{AUCpre}] \times 100$$

Data analysis

The data were assessed for a normal distribution using the Kolmogorov-Smirnov test (P>0.05). A dependent t-test in parametric statistics was used to compare mineral density between the pre and post-test within the SDF group and control group. The percentage of remineralization every 10 µm through the depth of the lesion in the silver diamine fluoride (SDF) and the control groups were compared using the Mann-Whitney test. Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) with a significance level set at 0.05.

4. Results and Discussion

4.1 Result

Eighteen incisor primary teeth were selected in this study according to the inclusion criteria. The mean depth of the artificial carious lesions of the enamel was 60 µm.

The authors used Micro CT to evaluate mineral density at pre and post-experimental periods. Figure 2; In the first row shows **a** Micro CT image of pre-test mineral density. The radiolucent area on the enamel surface represents artificial caries of initial lesions in the control and SDF group. The second row is the Micro CT image of post-test mineral density. The radiopaque area in the SDF group was seen as remineralization more than in the control group.

The mean mineral density of the pre-test was evaluated after creating artificial carious lesions and ranged from 0.55±0.19 to 0.64±0.22 g/cm^3. The mean mineral density of the post-test was evaluated after the pH-cycling and ranged from 0.66±0.24 to 0.78±0.24 g/cm^3 (Table 2).

The data of difference in the mineral density between pre and post-test of the SDF group showed a normal distribution in the Kolmogorov-Smirnov test ($p > 0.05$). The post-test mineral density in the SDF group was significantly higher than the pre-test mineral density using the Dependent t-test ($P<0.05$). However, the data of difference in the mineral density between pre and post-test of the control group did not show the normal distribution in the Kolmogorov-Smirnov test ($p < 0.05$). Wilcoxon Signed Ranks test was used to compare and showed no significance between pre and post-mineral density in the control group ($P>0.05$).

The mean percentage of remineralization of SDF and control group were 46.75 ± 35.27 and 2.21 ± 9.40, respectively (Table1). The Kolmogorov-Smirnov test showed that the percentage of remineralization every 10 µm depth did not show the normal distribution ($p < 0.05$). The Mann-Whitney test was used to compare the mean percentage of remineralization between each group. The significance level was set at 0.05. The comparison of the mean percentage of remineralization between the groups found that the SDF was significantly higher than the control group (Table 2).

Figure 3 Graph showed the mean mineral density compared between the pre and post-test of the SDF group and the control group. The authors observed that the mineral density of the SDF group increased higher than that of the control group.

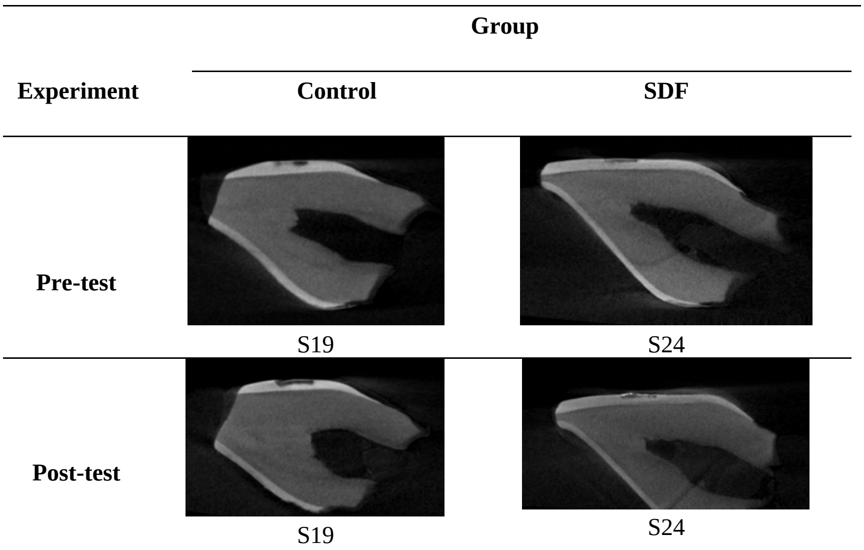

Figure 2 Picture of the mineral density pre and post-test from the Micro CT

Table 2 Mean mineral density of the groups at post-test and mean remineralization percentage of the groups

Group	N	Mean mineral density (g/cm3) ± SD		Within-group *p*-Value	Mean% Remineralization±SD	p-Value Between groups
		Pre-test	Post-test			
Control	9	0.64±0.22	0.66±0.24	0.089	2.21±9.40	0.000*
SDF	9	0.55±0.19	0.78±0.24	0.000*	46.75±35.27	

*significant difference (p<0.05)

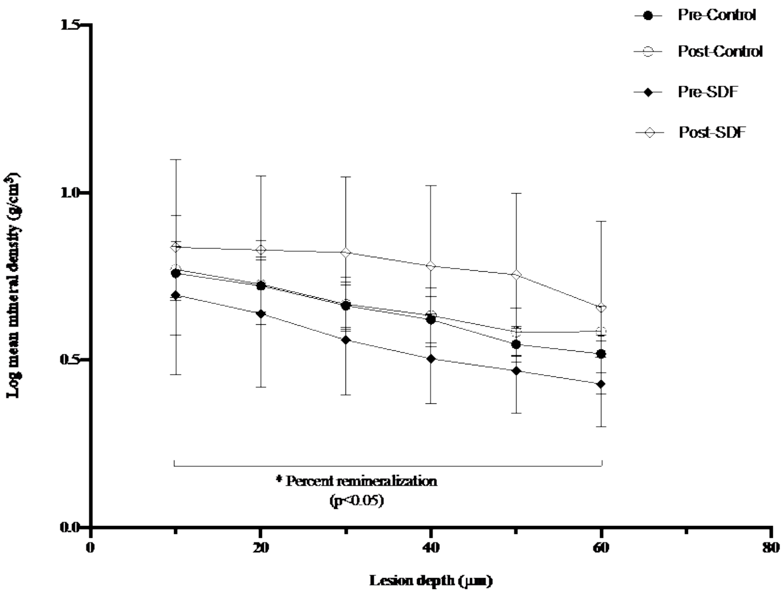

Figure 3 Graph showing the mean mineral density of both groups in pre and post-test.

4.2 Discussion

Silver diamine fluoride (SDF) is professionally used topical fluoride and suitable for cavitated carious lesions (Crystal et al., 2017). This study purposed to evaluate changes in mineral density on an artificial incipient caries of primary teeth enamel after applying SDF. Another purpose was to compare the percentage of remineralization after the application of SDF with the control group.

There are many methods to determine enamel remineralization including polarizing microscopy (PM), scanning electron microscopy (SEM), microhardness tester, transverse microradiography (TMR), and Micro CT. PM is accurate, less expensive, but time-consuming to prepare thin specimen sections and does not provide quality of mineral change of lesion (Rirattanapong et al., 2016, 2017). SEM uses to evaluate the morphological surface presented in the 3D topographical image. Microhardness tester is easy, quick, and requires only a tiny area of the specimen surface. Using this technique, the specimen surfaces were impressed by a diamond indenter; a Knoop or Vickers. TMR is considered to be the standard for mineral density change measurement in two dimensions, however, this technique is destructive and time-consuming (Lo, Zhi & Itthagarun, 2010). According to many studies, Micro CT is a gold standard and also preserves the specimens. The advantages of using Micro CT are its three-dimensional structure analysis, non-destructive property, and capability allowing the specimens to be remeasured after the pH-cycling procedure (Punyanirun et al., 2018). Thus, the authors decided to use the Micro CT(Skyscan, Kontich, Belgium) in this study to verify the mineral density and calculate the percentage of remineralization as an effect of the SDF on artificial carious lesions. Our study found that the mineral density on an artificial incipient caries of primary teeth enamel after applying 38% silver diamine fluoride (SDF) group is significantly higher whereas not significantly in the control group. The percentage of remineralization of the 38% SDF group is significantly higher than the control group through all the artificial incipient enamel carious lesion depths of 60 μm. The result indicated that SDF has effectively remineralized the initial enamel lesion due to the mechanism and concentration of fluoride in SDF. Fluoride and silver ion in SDF reacts with hydroxyapatite in tooth tissue that forms calcium fluoride(CaF_2) and silver phosphate (Ag_3PO_4) as two major products in a basic environment. Calcium fluoride acts as a pH-regulated slowly releasing fluoride reservoir during the cariogenic condition. Silver phosphate acts as a reservoir of phosphate ions facilitating the formation of fluorapatite from calcium fluoride. Another product is hydrogen phosphate ions (HPO_4^{2-}) that also facilitates calcium fluoride to form fluorapatite (Nantanee et al., 2016). Besides, SDF has a high concentration of fluoride, containing 5% fluoride or approximately 44,800 ppm fluoride (AAPD, 2018).

The study of Mohammadi and Farahmand examined the effect of application of SDF and fluoride varnish on primary teeth enamel by evaluating surface microhardness and resistance to demineralization in an in vitro cariogenic challenge by the pH-cycling method. They found that SDF and fluoride varnish also has a similar effect to prevent demineralization in enamel carious lesions (Mohammadi and Farahmand, 2018).

Nantanee et al. have compared the percent mean mineral density changes of artificial early proximal carious lesions after the application of SDF and glass ionomer cement in situ. The result showed that both SDF and GIC increased in mean mineral density changes and no significant difference of mean mineral density changes among the two groups (Nantanee et al., 2015).

In our study, SDF showed greater remineralizing effects than NaF did in the results of the micro-CT assessment, which concurred with previous studies. Yu et al. evaluate the remineralizing effect of the adjunctive application of 38% SDF and 5% NaF varnish on artificial enamel caries lesions via various methods ie. scanning electron microscopy (SEM), energy dispersive spectroscopy (EDS), micro-computed tomography(micro CT). The study found that the adjunctive application of SDF with NaF varnish had presented higher fluoride percentages than NaF alone on enamel caries (Yu et al., 2018).

Furthermore, another study described the incidence of interproximal caries arrest following SDF and fluoride varnish in the primary dentition. In a low-caries risk population, SDF and fluoride varnish application two to three times in 12 months resulted in arresting 84% of interproximal carious lesion suggested in the dentin-enamel junction (Hammersmith et al., 2020).

Although SDF has beneficial in the remineralization of initial enamel carious lesion, it still has some drawbacks. SDF develops dark staining on carious enamel and dentin as a result of silver phosphate precipitation, innocuous pulpal, and oral soft tissue irritation, which are the clinical limitations of its uses (Chu & Lo 2008; Rosenblatt et al., 2009). This dark discoloration is permanent unless restored (Crystal et al., 2017). However, in parental perceptions and acceptance of SDF dark staining, it is more acceptable on posterior teeth than on anterior teeth. Although SDF on anterior teeth is esthetically unacceptable, most parents prefer the application of SDF to avoid the use of advanced behavioral guidance. Thus, a thorough informed consent is crucial when using SDF as a professional used topical fluoride for dental caries interventions (Crystal, Janal, Hamilton, & Niederman, 2017).

5. Conclusion

Silver Diamine Fluoride (SDF) can promote remineralization of an artificial initial carious lesion in primary teeth.

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