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RESEARCH ARTICLE

Silver Diamine Fluoride Compound for Dental Caries and Its Characterisation Using Microscopic Computed Tomography and Nanoindentation

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Background: In our study, a silver diamine fluoride (SDF) compound for the treatment of dental caries was synthesized to characterize its remineralization activity upon direct application to deciduous teeth. This study aimed to use microscopic computed tomography (microCT) and nanoindentation to evaluate whether SDF composite application could effectively arrest dental caries in five exfoliated primary molars.
Methods: Carious teeth were extracted and visually examined using quantitative photofluorescence devices (Qraycam and Qraypen™). After performing microCT, the SDF composite was applied to the teeth according to the manufacturer's instructions. The researchers exchanged and precipitated the irritant saliva once daily for 1 week. The teeth were sectioned longitudinally through the centers of the mesial and distal surfaces, embedded, polished, and measured using nanoindentation. Thereafter, microCT was repeated. Statistical analyses were performed using GraphPad Prism software.
Results: Following SDF composite application, a remineralized layer was observed on microCT images, and the hardness increased when measured using nanoindentation. We found that demineralized enamel presented with an increased number of irregular crystals in the deep carious lesion group compared with those in the shallow carious lesion group, resulting in a rougher surface.
Conclusion: The SDF composite may be used for remineralization of early caries and cessation of advanced caries in primary molars.

Key Words: Dental caries, Fluorides, Silver diamine fluoride

Introduction

1. Background

Dental caries is caused by the release of acids from microbes. Acid causes demineralization of inorganic matter and dissolution of organic matter in teeth. This results in cavitation on the tooth surface, which is treated by restoration. Dental caries remains the most challenging dental disease in children owing to behavioral issues. Although restorative strategies can help diminish cariogenic biofilm formation[1,2], recent studies have focused on alternative approaches involving tooth remineralization[3]. Remineralization is a natural recovery process that partially reforms demineralized crystals with calcium and phosphorous[4]. Fluoride is known to effectively remineralize decayed teeth and exert antibacterial effects[5].

Kanduti et al.[6] reported a low incidence rate of caries in the presence of increased fluoride concentrations. It has also been reported that increasing fluoride concentrations in the surface enamel increase the resistance of the tooth surface to dental caries[6]. Fluoride plays a major role in remineralization by providing the conditions necessary for

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calcium phosphate to be easily deposited on the tooth surface and increasing the volume of remineralization[7]. The Cochrane Group reported that 1,500-ppm concentrations of fluoride within 10 μm of the outermost layers of the enamel can reduce the formation of dental caries by 50%[8].

Fluoride varnishes Duraphat® (5% sodium fluoride) and Fluor Protector® (1% difluorosilane) are commonly used for the prevention of early childhood caries[9]. Silver diamine fluoride (SDF) is a fluoridated agent that started attracting attention when it was approved by the U.S. Food and Drug Administration in 2014 to treat tooth sensitivity. It has also been found to have a strong remineralization effect and antibacterial action against caries-inducing bacteria[10,11]. According to Kim et al.[12] in 2020, the remineralization effect of SDF was greater than that of conventional 5% sodium fluoride varnish and a 5% sodium fluoride adhesive film, and the difference in the remineralization effect was larger, especially in deeper carious lesions. Therefore, it is expected that SDF will be able to further expand the applications of fluoride, which were previously limited to the treatment of shallow caries in enamel only[12]. A 38% SDF compound is commonly used to arrest caries in primary teeth, especially in younger children who are difficult to manage. The application of SDF to arrest dental caries is a noninvasive, quick, and simple procedure[13].

In this study, we aimed to reveal the in vitro remineralization effect of an SDF composite with the highest available surface fluoride concentration. We hypothesized that SDF composite application before and after tooth exfoliation would result in remineralization of tooth surfaces.

2. Objectives

This study aimed to use microscopic computed tomography (microCT) and nanoindentation to evaluate the remineralization effect of SDF composites in arresting dental caries in exfoliated primary molars of a Korean child.

Materials and Methods

1. Ethics statement

The local independent ethics committee of Wonkwang University approved the study (approval number: W1713/001-001). The patient's parents provided written informed consent.

2. Study design

Five primary molars (#54, #64, #74, #84, and #85) were extracted from a 9-year-old boy on the same day in the Department of Pediatric Dentistry at Wonkwang University Daejeon Dental Hospital. All surfaces of the extracted teeth were examined visually using quantitative photofluorescence devices (Qraycam and Qraypen™; AIOBIO, Seoul, Korea) to confirm the diagnosis of early proximal caries[14]. Among the various fluoride products, the SDF composite has the highest fluoride content (ppm), as shown in Table 1[15].

Table 1. Preparation Ratio with Fluoride Amounts (in ppm F Unless Otherwise Noted) Found in Common Fluoride Delivery Systems

Delivery system	Fluoride amounts
Water fluoridation	0.5～1.0
Fluoridated salt	250
Fluoridated milk	2.5～5.0
Fluoride drop, tablet, or chewing gum	0.25 mg per drop, tablet, or pellet
Fluoride mouthrinse	200 (daily), 900 (weekly)
Fluoride toothpaste	250～600 (children), 1,000～1,500 (adult)
Fluoride tooth mousse	1,100 (0.11% NaF)
Fluoride gel	1,000 (0.4% SnF_2)～20,000 (2% NaF)
APF gel/foam	12,300 (1.23% NaF)
Fluoride solution	4,840 (2% SnF_2)～19,360 (8% SnF_2)
Fluoride varnish	22,600 (5% NaF)
Sliver diamine fluoride solution	44,800 (38% $Ag(NH_3)_2F$)

APF: acidulated phosphate fluoride, NaF: sodium fluoride, SnF_2: stannous fluoride, $Ag(NH_3)_2F$: silver diammine fluoride.
Reused from the article of Chu et al. (Gen Dent 58: 37-43; quiz 44-5, 79-80, 2010)[15].

After imaging using microCT (Sky-Scan 1172TM; Sky-scan, Kontich, Belgium), SDF was applied to the teeth according to the manufacturer's instructions. Researchers exchanged and precipitated irritant saliva once a day for 1 week, after which microCT was performed again.

3. Measurement and characterisation

Optical reflection and photoluminescence (PL) images were obtained using a scanning optical microscope equipped with a spectrometer (FEX Modulized Confocal Raman Spectrophotometer, ACTTR, New Taipei City, Taiwan). White LED light and a 531-nm laser were used as illumination sources to obtain the reflection and PL images, respectively. The measurements were performed in a confocal micro-configuration using a 5× microscope objective lens and a motorized stage with a step size of 100 μm. Using a 300-groove/mm grating and a confocal pinhole of 100 μm, a spectral resolution of almost 0.36 nm was achieved. At each point in the images, PL intensities between 533 and 800 nm in each spectrum were integrated and used as representative values[16].

The teeth were first sectioned longitudinally along the centers of the mesial to distal surfaces, embedded, polished, and measured using nanoindentation. The hardness of each area was determined by nanoindentation tests using a continuous stiffness measurement (CSM) method[17]. Nanoindentation tests were conducted using a nanoindenter (iNano; KLA-Tencor, Ann Arbor, MI, USA) equipped with a diamond Berkovich tip. A depth-controlled indentation technique was used in the CSM method, with a maximum indentation depth of 600 nm. The strain rate of primary loading was 0.05 s^{-1}. The cyclic displacement superposed on the primary loading and its frequencies were 2 nm and 100 Hz, respectively. A minimum of 16 points were measured for each area. At each point, the values between 100 and 600 nm in indentation depth were averaged and used as the representative hardness values. The tip area function was calibrated using fused silica. An Xflash 6I100 energy dispersive spectrometer (BRUKER, Billerica, MA, USA) attached to Aproo SiVac field emission scanning electron microscope (Thermo Fisher Scientific, Waltham, MA, USA) was used for the analysis at an accelerated voltage of 15 kV and working distance (WD) of 8.5 mm.

4. Statistical analyses

Statistical analyses were performed using GraphPad Prism software (GraphPad, Inc., San Diego, CA, USA). All experiments were performed in triplicate. Values are expressed as means±standard deviation.

Results

In this experiment, microCT was used to evaluate the relighting effect of fluorophores, which is a noninvasive method and has the advantages of a less than 1% error rate and resolution in the range of 5～30 mm[18,19]. First, we evaluated the microCT results (SkyScan 1172^{TM}). After

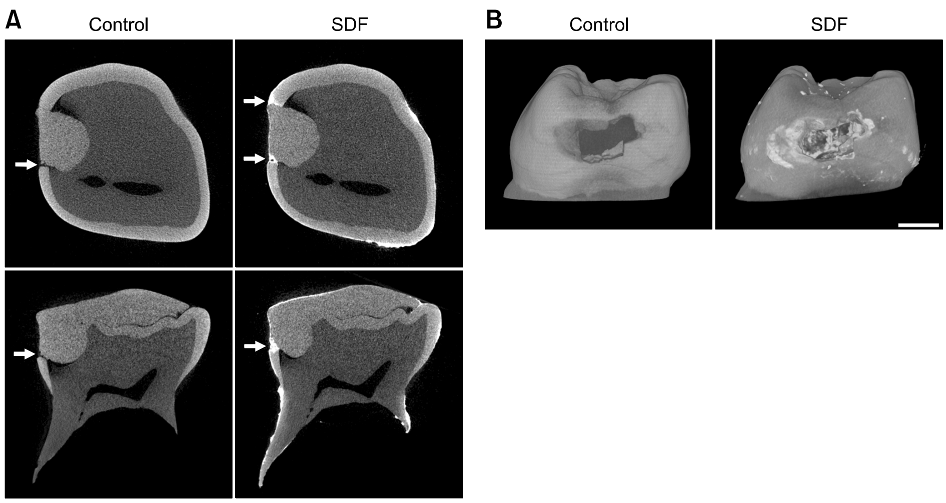

Fig. 1. Analysis of silver diamine fluoride (SDF) application effects using microscopic computed tomography (microCT). (A) Two-dimensional reconstructed coronal and horizontal slice images. A small defect before SDF application (arrows on the left) is remineralized after application (arrows on the right). (B) Three-dimensional reconstructed microCT image showing dental caries and remineralization after SDF application. Scale bar, 2 mm.

applying 38% SDF (Riva Star; SDI, Bayswater, Australia), a remineralized layer was observed by microCT. Furthermore, an increase in hardness was observed through nanoindentation. A microCT image of the maxillary right primary first molar (#54) showed that less soluble or virtually insoluble calcium fluoride, silver phosphate, and silver protein formed and precipitated on the dentin surface when SDF was applied. The same was true for the maxillary left primary first molar (#64) and mandibular left primary first molar (#74). Complete remineralization did not occur in any of the extremely large defects; however, partial recovery was observed, as shown in Fig. 1. These results were used to compare the degree of tooth remineralization. We found that microCT can quantitatively evaluate the density change in the same specimen before and after remineralization while providing more accurate information than conventional analysis methods, which can be used to evaluate only a portion of different specimens.

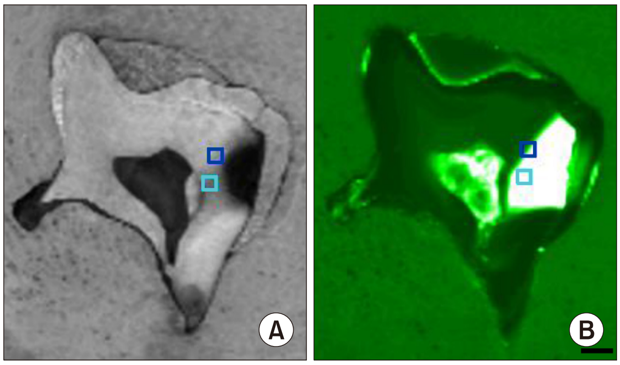

Fig. 2. Scanning optical microscopy and spectroscopy. (A) Reflection images. (B) Fluorescence images. Scale bar, 1 mm.

Varnish fluoride rearranges ions in carious lesions to create an appropriate concentration gradient for fluoride to diffuse inside and reduce the porosity of the body of the lesion[20]. We obtained fluorescence images (Fig. 2) using RAMEN equipment to trace the SDF penetrating the dentinal region of the carious lesions. Fig. 2 shows the reflection and fluorescence images of the specimen. The fluorescence image is an additional view of the fluorescence reaction in the area where increased hardness was detected by scanning optical microscopy and spectroscopy images of dental caries, displaying three different anatomical zones of enamel caries (translucent zone, body of the lesion, and surface zone) in the tooth. The distribution of phosphate across enamel caries was quantitatively shown.

The microscopic analysis of a specimen with proximal caries is shown in Fig. 3. Microscopic analysis indicated remineralization of the demineralized area and hardening of the dentinal tubules after SDF application. Fig. 3 (a and b) show normal dentin, which is normally covered with highly mineralized and protective enamel in the crown of the tooth. At the root of the tooth, dentin is covered by cementum, a structure that allows the attachment of the tooth to its respective bony socket. Underneath the dentin is the non-mineralized dental pulp, which is a connective tissue containing nerves and blood vessels. The surrounding tissues include the periodontal ligament and bony socket as a whole[21]. Fig. 3 (c-e) show demineralization due to carious lesions penetrating the enamel and dentin.

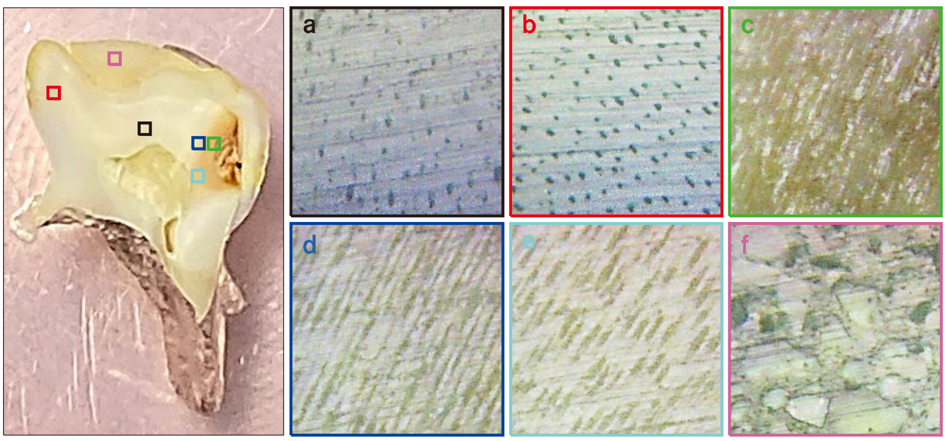

Fig. 3. Microscopic analysis of a target tooth with proximal caries (#54). Progressive magnification were used (of 10× to 50×), in order to acknowledge surface characteristics. a and b represent normal dentin, and f represents the filling material (glass ionomer cement). The remaining three panels c-e show demineralization due to dentin carious lesions, and panels d and e depict the post- silver diamine fluoride (SDF) application.

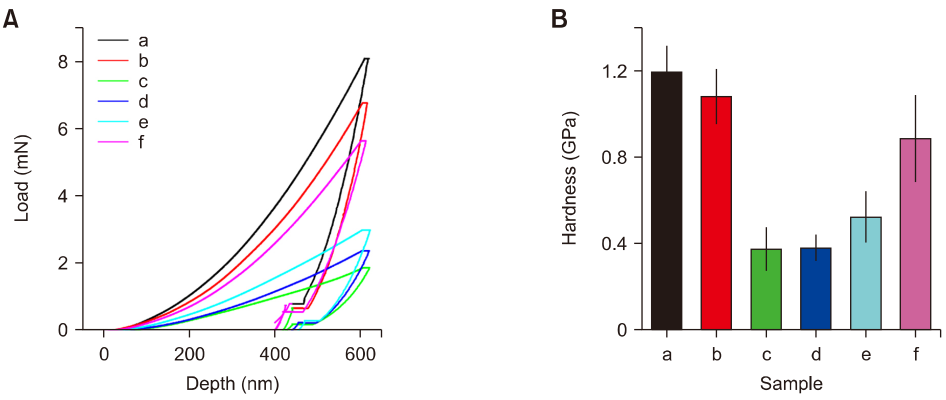

Fig. 4. Relationship between load and depth during hardness indentation of target tooth sites. (A) Hardness at fixed load-depth increases. (B) a and b represent the normal dentin; c–e represent carious dentin surfaces; and f represents the filling material.

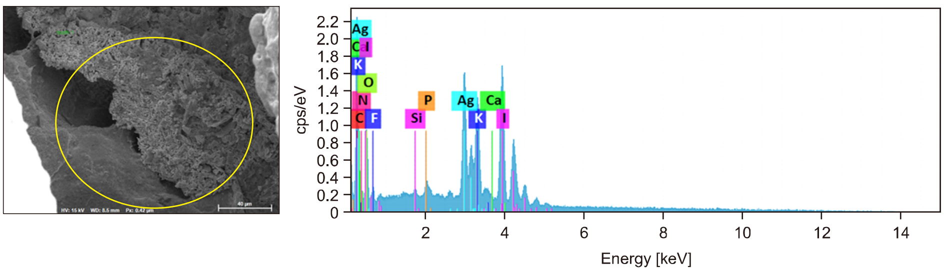

Fig. 5. Scanning electron microscopy-energy dispersive spectroscopy analysis (×200,000).

Fig. 4 shows the load–displacement curves for each tooth area obtained from the nanoindentation experiments. The characteristics of the load–displacement curves for sound enamel, sound dentin, and carious areas were similar. In the demineralized region of the tooth, the displacement was higher in areas where the SDF composite was applied (Fig. 4B, d and e) than in areas where it was not applied (Fig. 4B, c). Previous studies have also reported that SDF treatment increases the microhardness of carious dentin[22,23]. Microhardness analysis has been used to assess the loss and reincorporation of minerals into dental tissue because the reduction in the numerical hardness value is linearly related to mineral loss. Among the various microhardness tests, the Knoop microhardness analysis is specifically correlated with the amount of mineral loss from the tooth structure. The microhardness values from various areas of dentin were found to be significantly different using the Knoop microhardness analysis. This may be due to the differences in the inorganic compositions at different locations. The hardness of dentin also depends on the state of mineralization of the tissue[24].

To determine how regions d and e differed from regions a, b, c, and f, scanning electron microscopy–energy dispersive spectroscopy (SEM-EDS) analysis was performed. Fig. 5 depicts the SEM images of sound dentin, which is characterized by dentinal tubules of uniform shape and size with homogeneous peritubular and intratubular dentin. This well-defined structure of thedentin was destroyed after irradiation, resulting in the shrinkage and/or occlusion of the dentin tubule. Because silver ions were found more abundantly in regions e and d, it was theorized that silver particles penetrated these areas of the lesion and caused an increase in hardness. Fig. 5 shows that the chemical components observed through the SEM-EDS analysis included silver, fluoride, iodine, calcium, and nitrate.

Discussion

1. Interpretation

A recent systematic review by Jabin et al.[25] concluded that the use of 38% SDF is an effective method for arresting early childhood caries. SDF is a colorless, basic liquid made by combining silver nitrate and fluoride, with approximately 24∼28% (weight/volume) of silver, 5∼6% (weight/volume) of fluoride, and approximately 8% of ammonia[26]. Silver has antimicrobial effects, fluoride promotes remineralization, and ammonia plays a role in stabilizing high concentrations of the solution[27]. To determine how regions d and e differed from regions a, b, c, and f, SEM-EDS analysis was performed. Fig. 5 depicts the SEM images of sound dentin, which is characterized by dentinal tubules of uniform shape and size, with homogeneous peritubular and intratubular dentin. This well-defined structure of the dentin was destroyed after irradiation, resulting in the shrinkage and/or occlusion of the dentin tubules[28].

The results of this experiment show that SDF can be effective even in deep carious lesions; therefore, it is expected to expand the indications of fluoride compounds in the treatment of dental caries. Through SEM, we found that demineralized enamel presented with an increased amount of irregular crystals in the deep carious lesion group when compared with that in the shallow carious lesion group, resulting in a rougher surface.

2. Comparison with previous studies

A systematic review concluded that SDF arrested 81% of active carious lesions, and no significant complications were reported, except for black staining of the arrested lesion[15]. Thus, 38% SDF is effective in arresting caries in children[29]. A 2016 World Health Organization report on public health interventions against early childhood caries concluded that SDF can arrest dentinal caries in primary teeth and prevent recurrence after treatment[30,31]. America and Japan have subdivided SDF protocols into categories based on indications, methods of application, and post-operative instructions[32,33]. In Korea, SDF is rarely used; however, its effectiveness in preventing dental caries has been acknowledged. Although several studies have shown that a specific number of SDF applications is effective, there is no consensus on the number and frequency of SDF applications required to successfully arrest caries. Further studies are required to develop evidence-based guidelines for its use.

3. Limitations

There is a limitation to the research conducted by selecting products centered on materials currently used in dental clinics. The teeth of many patients could not be used as study material.

4. Suggestions

The effects of SDF on the arrest of dental caries have been demonstrated using both microscopic and spectroscopic methods. SDF may be used to remineralize early caries and arrest advanced caries in primary molars. We suggest that SDF composites can be applied for remineralization of early caries and cessation of advanced caries in primary molars. However, further research, including preclinical trials, is required to develop specific clinical application protocols.

Notes

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The local independent ethics committee of Wonkwang University approved the study (approval number: W1713/001-001). The patient's parents provided written informed consent.

Author contributions

Conceptualization: Youn-Soo Shim and So-Youn An. Formal analysis: Youn-Soo Shim and So-Youn An. Funding acquisition: None. So-Youn An. Investigation: Myung-Jin Lee, Min-Kyung Kang, and So-Youn An. Methodology: Min-Kyung Kang. Project administration: So-Youn An. Supervision: So-Youn An. Validation: So-Youn An. Visualization: Min-Kyung Kang. Writing – original draft: Youn-Soo Shim. Writing – review & editing: Myung-Jin Lee.

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Data availability

The silver diamine fluoride compound (SDF) data can be obtained here: https://www.mfds.go.kr.

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