Influence of ion-releasing filler-containing gel application on dentin remineralization by using ultrasonic velocity measurement

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Abstract: *Purpose*: The main objective of this study was to investigate the efficacy of S-PRG filler-containing gel application in promoting dentin remineralization using ultrasonic velocimetry.

Methods: Root dentin slabs of bovine teeth were sliced and formed into rectangles, treated with 0.1 M lactate buffer (pH 4.75) for 10 min, and then immersed in artificial saliva (pH 7.0). This treatment was repeated three times a day for 28 days. S-PRG filler-containing gel (PRG) and high-fluorine concentration silver diamine fluoride (SDF) solution were used. The treatment methods were: 1) untreated group, 2) PRG one-off application group, 3) SDF one-off application group, 4) PRG frequent-time application group, and 5) SDF frequent-time application group. After treatment, dentin slabs were soaked in 0.1 M lactate buffer solution and dipped in artificial saliva. This treatment was repeated 3 times a day for 28 days.

Results: The ultrasonic velocity of the untreated samples decreased slightly during the experimental period. In the one-off application group, ultrasonic velocities of SDF and PRG increased rapidly on day 7 and then decreased slightly during the experimental period. In the frequent-time application group, ultrasonic velocities of SDF and PRG increased during the experimental period; specimens treated with SDF had significantly higher ultrasonic velocities on each measurement day compared to specimens treated with PRG.

Conclusion: From the results of this experiment, it was concluded that the S-PRG filler-containing gel and silver diamine fluoride solution appear to promote remineralization and inhibit dentin demineralization.

Keywords: S-PRG filler, dentin, remineralization, ultrasonic measurement

イオン徐放性フィラー含有ゲルが象牙質の再石灰化に及ぼす影響に関する超音波測定による検討

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要旨：目的：S-PRG フィラー含有ゲル塗布による象牙質の再石灰化促進効果を超音波流速計を用いて検討した。

方法：ウシ歯根部象牙質板を長方形にスライスし，0.1 M 乳酸緩衝液（pH 4.75）で10分間処理した後，人工唾液（pH 7.0）に浸漬した。この処理を１日３回，28日間繰り返した。試片の処理は，S-PRG フィラー含有ゲル（PRG）とフッ化ジアンミン銀（SDF）溶液を用い，1）未処理群，2）PRG 単回塗布群，3）SDF 単回塗布群，4）PRG 頻回塗布群および 5）SDF 頻回塗布群とした。処理後，象牙質板を0.1M 乳酸緩衝液に浸漬し，人工唾液に保管した。この処置を１日３回，28日間繰り返した。

成績：未処理試料の超音波速度は，実験期間中にわずかに低下した。単回塗布群では，SDF と PRG の超音波速度は７日目に急激に上昇し，その後実験期間中にわずかに低下した。頻回塗布群では，SDF と PRG の超音波速度は実験期間中に増加した。SDF で処理した試料は，PRG で処理した試料と比較して各測定日の超音波速度が有意に高かった。

結論：本実験の結果から，S-PRG フィラー含有ゲルおよびフッ化ジアンミン銀溶液は再石灰化を促進し，象牙質の脱灰を抑制することが示された。

キーワード：S-PRG フィラー，象牙質，再石灰化，超音波測定

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Introduction

Evidence-based root surface caries prevention guidelines have been proposed for the management of root surface caries, including control of dietary carbohydrate intake, improvement of oral hygiene, antibacterial agents, fluoride-containing dentifrice, casein phosphopeptide-stabilized amorphous calcium phosphate, and application of bioactive glasses [1]. It is believed that the use of fluoride is a noninvasive and effective treatment to control root surface caries [2]. Mechanical tooth cleaning with the use of fluoridated gels is a cost-effective means of cleaning the tooth surface because it combines the mechanical destruction of dental biofilm with the addition of fluoride. Root surfaces have a higher affinity for fluoride uptake than enamel, but dentin is more easily dissolved in the acidic environment of cariogenic plaque than enamel, with the critical pH of cementum and dentin being 6.0 to 6.8 rather than 5.2 for enamel [3].

Root surface caries can occur in young adults but is more frequent in the populations [4]. This is the result of a longer lifespan that presents favorable conditions for the maintenance of natural teeth. Furthermore, root surface caries is often related to gingival recession. Due to the rough, retentive anatomy of the root surface and the difficulty of adequate cleaning, biofilm can easily accumulate, which may increase the risk of root surface caries development and progression [5]. Fluoride plays an essential role in preventing demineralization, and fluoride-containing products such as dentifrice, gels, mouthwashes, coatings, and sealants are widely used.

Silver diamine fluoride (SDF) has been employed in dentistry for more than 50 years, and studies on its efficacy are promising; SDF solutions have been reported to be an effective treatment to arrest dental caries and are usually recommended for children at high risk of developing caries [6]. According to a recent systemic review, annual application of 38% SDF in aged patients reduced incidences of new caries on exposed root surfaces by at least 50%, and longer-term interventions were more effective [7]. In clinical trials, various concentrations were applied and it was found that the 38% solution was significantly more effective in arresting caries than the 12% SDF or no application [8]. It was found that when SDF was applied to teeth, it penetrated the enamel and dentin and provided two to three times more fluoride storage under the tooth surface than with other fluoride solutions [9]. However, one of the main drawbacks of SDF is that it discolors the tooth surface. The use of biofunctional materials, especially those containing calcium and phosphate ions, has been introduced as a strategy to facilitate remineralization and improve fluoride uptake in dental substrates [10]. Surface-reaction prereacted glass ionomer (S-PRG) filler is prepared by acid-base reaction of fluoroboronaluminosilicate glass with polyacrylic acid in the presence of water, the preliminary product being a stable glass ionomer phase within the glass particles. It is reported that the S-PRG inhibits tooth demineralization and plaque formation by releasing fluoride (F^-), borate (BO_3^{3-}), strontium (Sr^{2+}), silica (SiO_3^{2-}) sodium (Na^+), and aluminum (Al^{3+}) ions. As a matter of fact, compared to fluoroaluminosilicate glass fillers, resin composites with SPRG fillers were shown to release F^- at a higher rate [11]. In the previous report [12], S-PRG filler also has the effect of modulating the acidity of the oral cavity, making the pH of the surrounding environment slightly alkaline upon contact with water or acidic solutions. It is thought that this effect is mediated by ions released from the S-PRG filler [13].

There are individual reports of effects on tooth remineralization using fluoride-containing agents, but few reports have compared them. The principal purpose of this study was to demonstrate the efficacy of S-PRG filler–containing gel application on the prevention of dentin remineralization by using ultrasonic measurement method. The null hypothesis tested was that there were no differences among the samples treated with the S-PRG filler containing gel and the SDF solution.

Materials and Methods

1. Specimen preparation

In this study, oral gel containing S-PRG filler (PRG; PRG Pro-Care Gel; Shofu, Kyoto, Japan) and a high fluoride concentration SDF solution (Saforide; Toyo Pharmaceutical, Osaka, Japan) were used (Table 1).

Incisor of freshly extracted bovine teeth were cleaned and stored in physiological saline solution for up to 2 weeks. About two-thirds of the root apex structure of each tooth was removed using a diamond-impregnated disk in a low-speed saw (IsoMet 1000 Precision Sectioning Saw; Buehler, Lake Bluff, IL, USA). Surfaces of root dentin were polished with wet #240-grit silicon carbide (SiC) paper (Fuji Star Type DDC; Sankyo Rikagaku, Saitama, Japan) to expose flat dentin surfaces. Dentin blocks were shaped carefully into rectangles (4×4×

Table 1　Materials used in this study and their compositions

Material (Lot No.)	Code	Composition	Manufacture
Saforide (808RA)	SDF	38% silver diamine fluoride	Toyo Pharmaceutical, Osaka, Japan
PRG Pro-Care Gel (4G0011)	PRG	hydrated silica, S-PRG filler, glycerol, carboxymethylcellulose sodium, sorbitol, sodium dodecyl sulfate, mint flavoring	Shofu, Kyoto, Japan

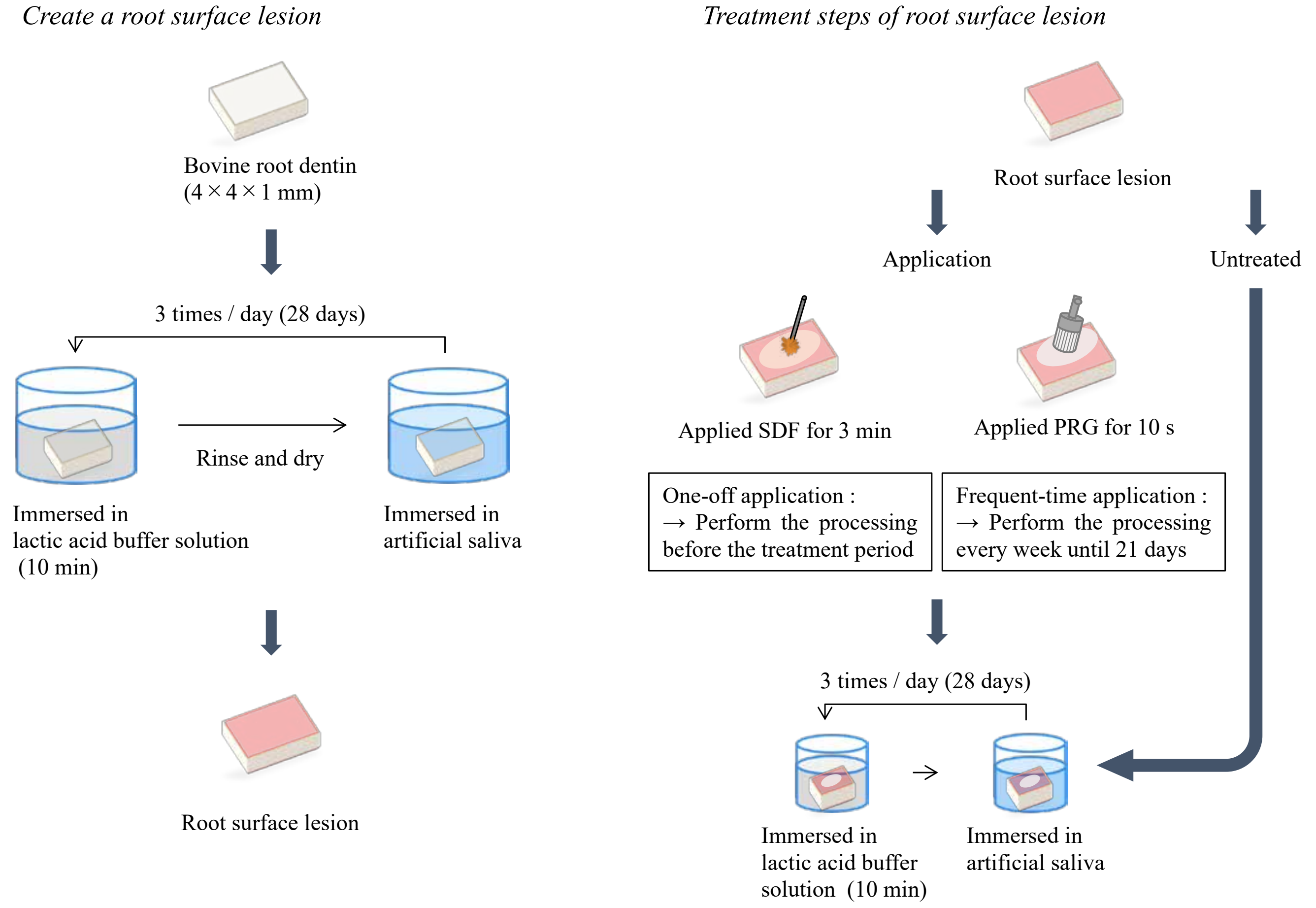


Fig 1. Specimen preparation and study design of the experiment.

1mm) using a super-fine diamond point (SF106RD; ISO #021a, Shofu). The surfaces of the specimens were successively polished with #600, #1,200, and #2,000 grit size wet SiC paper. The thickness and size of the specimens were measured using a dial gauge micrometer (CPM15-25DM; Mitutoyo, Tokyo, Japan) and covered with wax except for the labial side of the dentin slab on the treated surface.

All specimens were treated with undersaturated 0.1 M lactic acid buffer solution (pH 4.75, 0.75 mM $CaCl_2 \cdot 2H_2O$, and 0.45 mM KH_2PO_4) for 10 min and then placed in artificial saliva (pH 7.0, 14.4 mM NaCl, 16.1 mM KCl, 0.3 mM $MgCl_2 \cdot 6H_2O$, 2.0 mM K_2HPO_4, 1.0 mM $CaCl_2 \cdot 2H_2O$, and 0.10 g/100 mL sodium carboxymethyl cellulose) at 37℃. These procedures were conducted three times daily (with an 8 h interval time) over 28 days. The specimens were then divided into five different treatment groups of 10 specimens each (Fig. 1).

1) Untreated: The cells were treated with 0.1 M lactate buffer for 10 min and then immersed in artificial saliva. This procedure was repeated three times. The specimens were then subjected to acid challenge for the duration of the experiment.
2) One-off application with PRG: PRG was applied with a soft brush for 10 s, rinsed with tap water, and dipped in artificial saliva. The specimens were then subjected

to acid challenge for the duration of the experiment.

3) One-off application with SDF: SDF was applied with a microbrush, allowed to stand for 3 min, rinsed with tap water. The specimens were then subjected to acid challenge for the duration of the experiment.

4) Frequent-time application with PRG: PRG was applied with a soft brush for 10 s, rinsed with tap water, This procedure was repeated once a week during the acid challenge experiment.

5) Frequent-time application with SDF: SDF was applied with a microbrush, allowed to stand for 3 min, rinsed with tap water.This procedure was repeated once a week during the acid challenge experiment.

PRG was applied using a micromotor handpiece (Torq tech CA-DC; J. Morita Mfg. Co., Ltd., Kyoto, Japan) and a soft brush (Merssage Brush Soft; Shofu) with a digital balance (AT200; Mettler-Toledo, Greifensee, Switzerland). The process was performed at 1,000 rpm and a constant pressure of 0.1 N while monitoring. These operations were performed by a single operator to ensure accuracy.

2. Ultrasonic velocity measurement

Ultrasonic velocity measurements were performed using a system comprising a pulse receiver (5900PR; Panametrics, Waltham, MA, USA), a longitudinal wave transducer (V112; Panametrics), and an oscilloscope (Waverunner LT584; LeCroy, Chestnut Ridge, NY, USA) (Figure 2). The instruments were initially calibrated by standard procedures using a 304 stainless steel calibration block (2211M; Panametrics, Inc.). Measurements were taken before the start of the study and on days 1, 7, 14, 21, and 28. All measurements were performed at 23 ℃ ± 1 ℃ and 50% ± 5% relative humidity.

Ultrasonic waves travel through the transducer into the sample and are either reflected at the surface or transmitted through the sample. The reflected wave that reaches the probe is termed the surface echo (S echo), while the transmitted wave reflected at the interface between the air and the back surface of the sample is termed the back surface echo (B echo). The time difference between the S and B echoes represents the time it takes for the wave to propagate through the sample (Figure 3). When the specimen thickness (T) is known, the acoustic velocity (C) can be calculated by measuring the difference time (Δt) between the S and B echoes using the following equation:

$$C = 2T/\Delta t$$

where C: acoustic velocity
T: thickness of the specimen
Δt: round trip transit time

Three measurement points were selected for each sample, and the average value was used as the specimen's ultrasonic velocity.

3. Statistical analysis

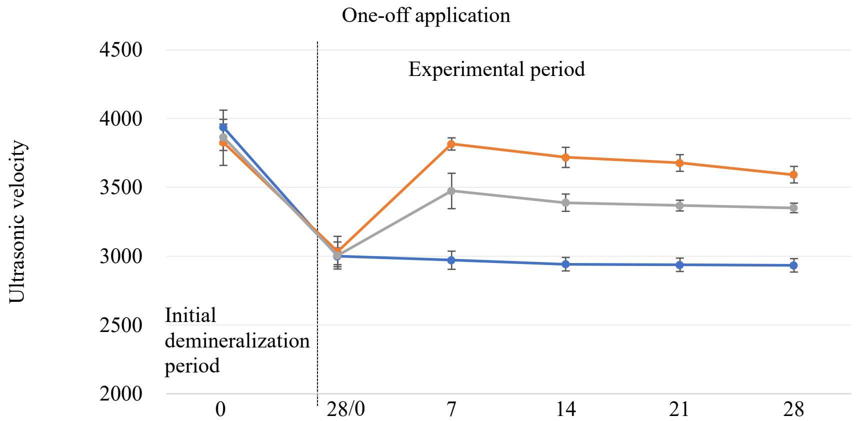
Data were analyzed using commercially available statistical software (Sigma Plot Ver. 13; Systat Software, Chicago, IL, USA). Data for each group were first tested for homogeneity of variance using the Bartlett test, tested for normal distribution using the Kolmogorov-Smirnov test, and then analyzed using repeated measures analysis of variance and the Tukey-Kramer post hoc multiple comparison test. The significance level was set at $\alpha = 0.05$.

Results

The average ultrasonic velocities in different treatment groups are shown in Figs. 2, 3. During the initial demineralization period, the ultrasonic velocities of all groups decreased. The differences in storage periods were greater than expected by chance after allowing for the effects of storage conditions, so multiple comparisons were done on the data. The average ultrasonic velocities of all groups in the initial deminerarization period decreased from 3938 to 3000 m/s. During the experimental period, ultrasonic velocity of untreated group gradually decreased from 2971 to 2934 m/s. In the one-off application specimens, the ultrasonic velocities of SDF and PRG increased dramatically on day 7 and then slightly decreased during the experimental period. For the frequent-time application specimens, the ultrasonic velocities of SDF and PRG increased during the experimental period. Specimens treated with SDF had a significantly higher ultrasonic velocity on each measurement day when compared with those treated with PRG.

Discussion

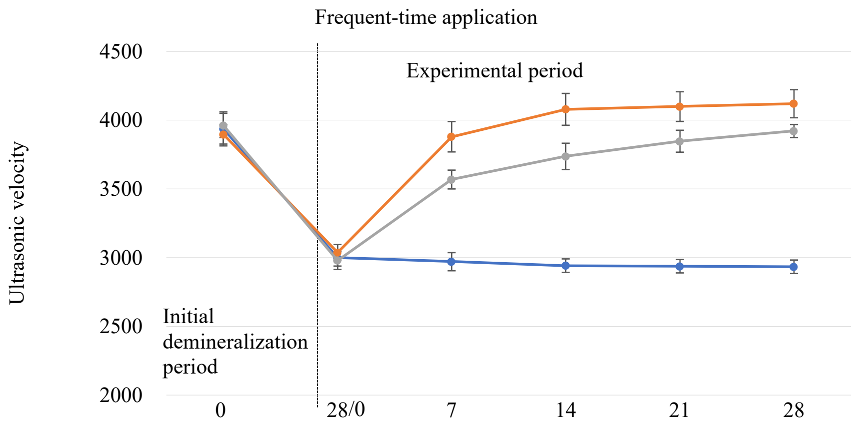
Dentin has a complex structure and comprised two major components, namely, collagen-based organic matrix and hydroxyapatite crystal. Collagen fibrils are woven and lie perpendicular to the tubules, whereas apatite crystals tend to be parallel to the long axis of the collagen fibrils. Regarding root surface lesions, it has been suggested that the anticaries effect of combining with fluoride is related to the intrinsic mineral and organic composition



	0	28/0	7	14	21	28
Untreated	3938 aA	3000 bA	2971 bA	2942 bA	2938 bA	2934 bA
SDF treated	3828 aA	3034 bA	3816 aB	3719 acB	3678 cB	3593 cB
PRG treated	3865 aA	3005 bA	3475 cC	3389 cdC	3368 cdC	3351 dC

Unit: m/s, n = 10 teeth per group.
Within groups, means with the same lower-case letter are not significantly different ($p \geqq 0.05$).
Between groups at the same periods, means with the same upper-case letter are not significantly different ($p \geqq 0.05$).

Fig 2. Changes in the ultrasonic velocity of one-off application groups.



	0	28/0	7	14	21	28
Untreated	3938 aA	3000 bA	2971 bA	2942 bA	2938 bA	2934 bA
SDF treated	3898 aA	3038 bA	3881 aB	4080 cB	4100 cB	4121 cB
PRG treated	3963 aA	2979 bA	3569 cC	3737 dC	3848 adC	3922 aC

Unit: m/s, n = 10 teeth per group.
Within groups, means with the same lower-case letter are not significantly different ($p \geqq 0.05$).
Between groups at the same periods, means with the same upper-case letter are not significantly different ($p \geqq 0.05$).

Fig 3. Changes in the ultrasonic velocity of frequent-time application groups.

comprising the root surface. Both clinical and laboratory studies have shown the role of fluoride in enhancing the resistance to or preventing cervical lesions [1]. Fluoride suppresses mineral loss from dentin during the acid dissolution process and enhances remineralization in a similar physicochemical manner as occurs in enamel. The availability of fluoride in saliva and plaque fluid is essential, even at low levels, to maintain the surface integrity of teeth and avoid the formation of subsurface caries [14].

Ultrasonic imaging is a non-invasive technique that offers considerable potential for diagnosis, as well as being a valuable research tool. Ultrasonic devices are also used to detect dentin demineralization [15], and to measure dentin thickness between the tooth surface and the pulp chamber [16]. Because the speed of sound (V) is sensitive to the viscoelastic properties of materials [17], ultrasonic devices can be used to monitor the setting process of resin cements. This method might also result in less variation than the visual-examination method, depending upon the examiner [18].

The results of this study indicated that the ultrasonic velocities of the SDF- and PRG-applied samples were faster than those measured in the untreated group. These changes might be due to the presence of SDF-derived F- and PRG filler-derived ions in the gels, which strengthened the eroded dentin surface and enhanced calcification [12]. Although both PRG and SDF were effective in increasing sound velocity, SDF had a predominantly greater effect. Thus, the null hypothesis tested was that there was no difference between the PRG and SD treated samples was rejected.

It has been shown that SDF confers remineralizing properties to dentin through preservation and protection of the collagen matrix [13]. SDF showed a greater protective effect against dentin demineralization compared to untreated samples, as detected by ultrasonic velocimetry, which further support the findings. Because SDF contains high concentrations of fluoride and silver, it is expected to be highly effective in preventing caries in root surface dentin. In addition to its anti-decalcification effect on the mineral phase, SDF has been reported to have a significant effect on dentin collagen fibers and may inhibit their degradation in an acidic environment [1]. SDF also exhibits very effective antimicrobial activity against cariogenic biofilms [14]. A systematic review consistently supports the effectiveness of SDF in preventing coronal caries in the deciduous dentition and in preventing and arresting root surface caries in the elderly [19]. In contrast, because dentistry is concerned with esthetics, the potential drawbacks of SDF need to be taken into account. Among its main drawbacks is that it causes discoloration, which occurs when silver ions in the composition of SDF are transformed into metallic silver in the presence of light and spread deep into the tooth [20]. A report evaluating how dental staining associated with SDF affects acceptance of this treatment among parents with young children [21]. The results suggest that many parents are willing to compromise esthetics in favor of less invasive treatment options when patients are not cooperating with conventional treatment methods. In adult patients, dentists and dental hygienists may be concerned about the esthetic consequences of stained lesions because dentin unaffected by caries does not stain.

The S-PRG filler behaves as a fluoride-releasing substance, and the combination of strontium and fluoride ions enhances the crystallinity of carbonated hydroxyapatite. The fluoride ions and silica ions released from the S-PRG filler in the gel may have contributed to the promotion of dentin remineralization. To promote tooth remineralization and prevent acid attack, fluoride uptake from the outer surface of the tooth is essential. Silica, among other ions released from S-PRG filler, may play an important role in dentin mineralization by promoting hydroxyapatite formation via induction of hydroxyapatite nucleation [22]. In aqueous environments, sodium ions (Na^+) with hydrogen cations (H^+ or H_3O^+) are exchanged rapidly from the solution. The migration of Ca^{2+} and PO_4^{-3} groups to the S-PRG fillers formed a $CaO–P_2O_5$-rich layer on the dentin surface that crystallized into hydroxycarbonate apatite [23]. Chemical reactions that promote apatite formation have been suggested to stimulate remineralization and possibly prevent demineralization of dentin [24]. Hence, the combination of fluoride and silica ions can inhibit the dissolution of dental minerals by acids produced by cariogenic bacteria. In addition, strontium acts as a substitute for calcium during precipitation and is thought to have a synergistic caries-inhibiting effect with fluoride [25]. Furthermore, reportedly, BO_3^{3-} and F^- released from resin composite containing S-PRG fillers exhibit inhibitory effects on the metabolic activities of *Streptococcus mutans* at concentrations lower than those that inhibit S. *mutans* growth [11].

Conclusions

Under the current experimental condition, using dentifrices containing PRG and SDF solution appear to promote remineralization of the dentin. For people with a low risk of caries, avoiding preventative effects may be most cost-effective, daily use of gel containing S-PRG filler might be suitable. Application of SDF is indicated for patients with extremely higher caries risk, those who cannot tolerate conventional dental treatment, patients who are medically compromised, and those in disparity populations with little access to care.

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Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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