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Original Article

Comparison of the Remineralization Effect of Nano Herbal Toothpaste With Two Kinds of Toothpaste Containing Fluoride and Bioactive Glass on Primary Enamel Lesions: An *In Vitro* Study

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Abstract

Background: Considering the therapeutic properties of the compounds used in Albodent Iranian toothpaste and little evidence about the effect of NovaMin toothpaste on primary caries lesions, the purpose of this research was to compare the effect of toothpaste containing fluoride and toothpaste containing bioactive glass with Albodent toothpaste on enamel remineralization in a laboratory manner.

Methods: Overall, 24 healthy human premolar teeth were selected and divided into buccal and lingual halves. The demineralization cycle of the samples was performed for 14 days. The samples were classified into four groups and were brushed twice a day for 28 days with tested toothpaste. A microhardness test was conducted, and changes in the enamel surface and morphology of one sample selected from each group were evaluated by scanning electron microscopy. The analysis of variance and Tukey's tests were used for the statistical analysis of the data.

Results: The average difference in microhardness in the studied groups was statistically significant ($P<0.05$) when compared two-by-two with the control group. The most noticeable difference was found in the comparison of the Sensodyne group with the control group, while the lowest difference was observed in the comparison of the Albodent group with the control group.

Conclusion: The presence of NovaMin in toothpaste along with fluoride can increase the efficiency of the remineralization rate of primary enamel lesions compared to fluoride toothpaste without bioactive glass. In addition, the effectiveness of herbal toothpastes, which do not contain essential artificial ingredients in the remineralization of primary enamel lesions was lower than that of non-herbal fluoride toothpastes.

Keywords: Primary carious lesions, Fluoride, NovaMin, Bioactive glass, Herbal toothpaste

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Background

Dental caries is the most common chronic non-communicable disease in the world, which has significant effects on public health and the quality of individual life (1). Caries is a dynamic process that is associated with alternating periods of demineralization and remineralization of the tooth structure (2). Recently, the elimination of dental disease in the early stages and non-invasive methods of remineralization of primary carious lesions by different materials have been supported (3). Anti-caries agents act non-invasively by inhibiting bacterial acid production or changing the balance of remineralization and demineralization (4). In the past few decades, several mechanisms have been described that inhibit dental caries, including fluoride (through toothpaste or mouthwashes), artificial sweeteners (sorbitol and xylitol), chlorhexidine gluconate products, and salivary flow stimulation (5). Fluoride has always been considered the gold standard for remineralization. However, its therapeutic capacity may have limitations, and its excessive use may have side effects such as fluorosis (6), toxicity at high doses, and the development of fluoride-resistant *Streptococcus mutans* and other oral bacterial species (4). These problems raise the need for preventive strategies that can be used alone or in addition to fluoride while ensuring higher safety (7). Bioactive glasses are utilized in dentistry in the fields of implants, periodontal bone regeneration, or the treatment of dentine hypersensitivity. These materials

have the potential to form an appetite layer and have been shown the ability to induce the mineralization of dentin surfaces (3). Bio-active glass is a biocompatible material whose clinical use in dentistry has increased during the last decade due to its unique mineral composition that is highly similar to bones and teeth.

The side effects and problems of fluoride raise the need for preventive strategies that can be employed alone or in addition to fluoride and have higher safety (generally due to controlled degradation over time, the released ions can react with body tissue and create various therapeutic effects such as repairing and regenerating bone and dental tissue). Recently, toothpaste containing various bioactive glass, such as NovaMin as active ingredients, has entered the market, but there is little information about the potential of remineralizing enamel and stimulating the remineralization of primary enamel caries lesions (3,5). Recently, herbal toothpaste has been presented due to the side effects of some components in chemical toothpaste and the acceptability and therapeutic properties of medicinal plants. Albodent, for example, is an herbal toothpaste that has various natural compounds such as stevia, cinnamon, brushwood, sumac, honey, and sea foam. In addition, this toothpaste does not contain sodium lauryl sulfate and harmful industrial preservatives that cause damage to human health (8-11). It seems that the wood of the toothbrush tree (Salvadora persica) is a suitable tool for oral hygiene due to the ability of its fibers to reach the dental surfaces and its chemical properties. This plant contains various mineral and chemical substances such as sulfur alkyds that have antibacterial properties and chloride and fluoride that can cause enamel remineralization (12). The sea floor is a hard structure in the body of cuttlefish, which is also used as a scaffold for bone due to its mechanical properties (13,14). This structure has sodium, potassium, magnesium, and calcium, which cause bone formation (15). Whole fish bone also contains calcium carbonate and pure hydroxyapatite, which makes it suitable for tissue engineering (16). Little evidence is available about the effect of NovaMin toothpaste on enamel lesions. Considering the therapeutic properties of the compounds used in Iranian Albodent toothpaste and the limited information about its effect on primary carious lesions, this study sought to compare the effects of toothpaste containing fluoride and toothpaste containing bioactive glass (the new Albodent toothpaste) on primary decay lesions and enamel remineralization in a laboratory manner.

Materials and Methods

In general, 24 healthy human premolars that were extracted for orthodontic reasons and periodontal problems within 3 months before the start of this study were gathered as test subjects. The collected teeth were observed to be free of caries, cracks, wear, and hypocalcification in clinical examination. The surfaces of the teeth were mechanically cleaned from debris and mass using a fluoride-free prophylaxis paste, a rubber cap, and a low-speed handpiece, and then examined by a stereomicroscope (Olympus, Shinjuku, Tokyo, Japan) with a magnification of X40 to ensure the absence of enamel decay lesions and cracks (17). The roots of the teeth were separated using a 007 long fissure bur and water cooling, 1 mm below the CEJ, then they were divided into buccal and lingual halves with a mesiodistal section to obtain 48 samples. Afterward, the anatomical crowns of the teeth were mounted on acrylic resin (Acropars, Iran) so that only the enamel surfaces were exposed to apply materials in the next steps. The surface of the enamel was rubbed and smoothed using waterproof silicon carbide paper grit 1200 (Struers Company, Germany) in 10 back-and-forth movements to obtain a suitable surface for the microhardness test (16). A demineralizing solution containing 0.05 M lactic acid, 2.2 mM calcium chloride, and 2.2 mM sodium dihydrogen orthophosphate was made, and potassium hydroxide pellets were added to stabilize the pH of the solution at 4.5 (16). To prepare artificial saliva, 3.90 mM sodium phosphate, 4.29 mM sodium chloride, 17.98 mM potassium chloride, 1.1 mM calcium chloride, 0.08 mM magnesium chloride, 0.05 mM sulfuric acid, and 3.27 mM sodium bicarbonate were used as the solution with a pH level of 7.2 (17). A remineralizing solution containing 1.5 mmol Ca^{2+} ($CaCl_2$), 0.9 mmol phosphate (KH_2PO_4), and 1 ppm fluoride (NaF) was utilized as well (2). The test procedure included placing the samples in a demineralizing solution (made in the biochemistry laboratory of Hamedan University of Medical Sciences) with a pH rate of 4.5 for 8 hours; then, the samples were placed in artificial saliva for 1 hour and in the remineralizing solution with a pH rate of 7 for 15 hours, respectively. This cycle was continued for 14 days to demineralize the enamel surface. Demineralizing and remineralizing solutions were changed every 2 days (18). The samples were then randomly divided into control, fluoride toothpaste (Colgate, MaxFresh, Poland), bioglass toothpaste (Sensodyne Repair and Protect, Ireland), and nanoherbal toothpaste (Albodent, Iran) groups (n = 12). After creating primary decay lesions, the samples were transferred into artificial saliva. Each sample was brushed twice a day (every 12 hours) with a soft toothbrush and paste for 28 days. The test subjects were brushed for 30 cycles of 15 seconds by a single operator. During brushing, the samples were immersed in the testing toothpaste slurry, which consisted of a mixture of 1 g of toothpaste in 5 mL of artificial saliva (3,5,17). Next, the samples were removed from the artificial saliva, dried, and subjected to a microhardness test with a microhardness tester microscope (Micrometer 1, Buehler, Lake Bluff, IL, USA). For each sample group, the Vickers diamond indicator was applied with a force of 200 g for 10 seconds to the incisal, middle, and cervical surfaces of each tooth crown, and the average of these three points was reported as the microhardness value for each sample (5). Afterward, one sample of each test group was selected for scanning electron microscope (SEM) evaluation, and the changes in the surface of the enamel, surface roughness, and morphology were

examined after coating with gold during the sputtering process (16).

Data Analysis

Using SPSS software (version 22), the normality of the data was checked by the Kolmogorov-Smirnov test. Due to the normal distribution of the gathered data, the mean value was used to describe the size of micro-hardness according to the study groups. A one-way analysis of variance (ANOVA) analysis was utilized to compare the average micro-hardness according to the studied groups. Then, two-by-two micro-hardness averages between the studied groups were compared with the post hoc multiple comparisons approach using the Tukey method. The significance level of the tests (*P* value) was considered < 0.05.

Results

Based on the Kolmogorov-Smirnov test results, it was determined that the distribution of microhardness was normal ($P = 0.98$). The difference between the average microhardness values of the studied groups was investigated with an ANOVA test. The results are reported in Table 1. Statistically significant differences were observed in all the studied groups ($P < 0.001$). Considering the significance of the ANOVA test, the micro-hardness averages of the studied groups were compared two-by-two with the post hoc multiple comparisons approach using the Tukey method (Table 2). The differences between the average value of micro-hardness for all three kinds of toothpaste were statistically significant ($P < 0.05$) in comparison with the control group. In addition, a two-by-two comparison of the averages of the intervention groups was performed with Tukey's test (Table 3).

To investigate the surface morphology of the enamel, SEM images were prepared with 500×, 1000×, 2000×, 10000× magnification of the surface of the samples. The micrograph image after the demineralized samples showed an irregular morphological surface with spaced crystals, which is part of the characteristics of the demineralized enamel structure. After the application of fluoride toothpaste on the demineralized enamel surface, SEM images demonstrated relatively small and abundant demineralized hydroxyapatite crystals between the spaces. In Sensodyne toothpaste samples, which contain fluoride and bioactive glass (NovaMin), relatively fewer granules were formed that filled the spaces (Figure 1). The granules were attached and revealed larger granules compared to Colgate toothpaste, which only contained fluoride. The interlocking granules formed a honeycomb structure, with one side attached to the hydroxyapatite crystal.

Table 1. Comparison of Average Microhardness (kg/mm^2) According to the Studied Groups

Study Groups	Number	Mean ± Standard Deviation	*P* Value[a]
Control	12	271.98 ± 20.79	< 0.001
Colgate	12	298.86 ± 23.45	
Albodent	12	294.33 ± 19.16	
Sensodyne	12	324.85 ± 21.37	

[a] ANOVA.

Table 2. The Results of the Two-by-Two Mean Comparison of the Intervention Groups With the Control Group Through Tukey's Test

Compared Groups	Difference in Averages	95% Confidence Interval	*P* Value
Colgate versus control group	26.88	3.72-50.04	0.017
Albodent versus control group	22.35	-0.81-45.51	0.062
Sensodyne versus control group	52.86	29.70-76.03	< 0.001

Table 3. The Results of the Two-by-Two Comparison of the Averages of the Intervention Groups With Each Other Through Tukey's Test

Compared Groups	Difference in Averages	95% Confidence Interval	*P* Value
Colgate versus Albodent	4.53	-18.63-27.69	0.953
Sensodyne versus Colgate	25.98	2.82-49.14	0.022
Sensodyne versus Albodent	30.51	7.35-53.68	0.005

Discussion

Several methods can interfere with the demineralization process, remineralization of the enamel structure, and reversion of the progress of carious lesions (19). Remineralization is considered a biological repair process that causes the deposition of calcium, phosphate, and other ions in the demineralized area in non-cavitary lesions. In addition to calcium and phosphate ions, fluoride also forms a new surface on the crystals in residual caries after remineralization (19). According to clinical evidence, fluoride can be effective in preventing the onset of caries, stopping, and possibly reversing the demineralization process (20). Fluoride is considered the most important and effective active compound to prevent and treat caries, which, in its ideal amount, reduces the incidence of dental caries, although excessive amounts of it can cause serious side effects such as dental or skeletal fluorosis (21). There has been growing skepticism about the use of fluoride in recent years. Therefore, studies on different remineralization agents that can have similar effects on caries prevention as fluoride but act safer than that have become highly important (20).

The key to the remineralization process of enamel and dentin is the availability of calcium in the oral environment, which has led to the development of calcium-based systems to enhance the availability of calcium and phosphorus (22). NovaMin (Bioactive glass) was initially used to treat dentine hypersensitivity. This substance is a white sodium phosphosilicate in the form of powder and is highly biocompatible, which can be utilized for the remineralization of the tooth structure (20,22,23). NovaMin releases calcium, sodium, phosphorus, and silica ions into the solution when it comes into contact with body fluids such as water or saliva, leading to the

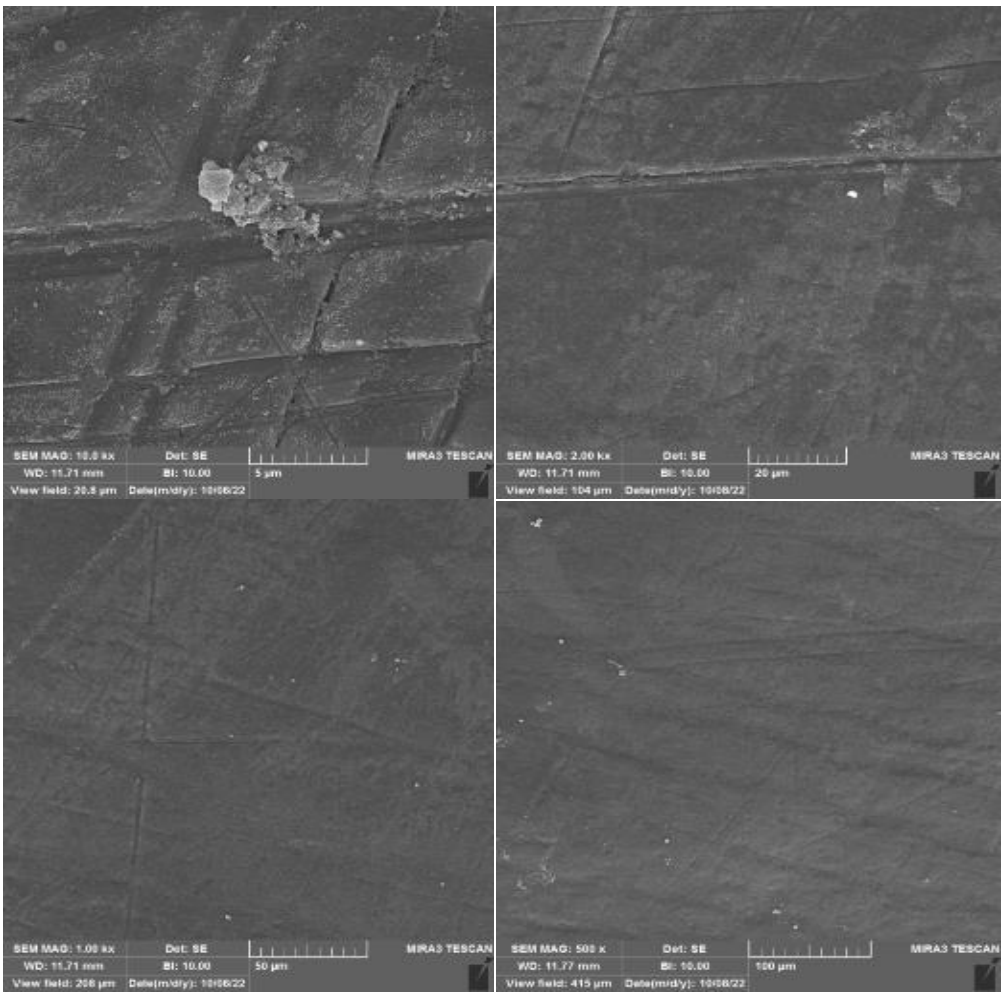

Figure 1. SEM Images of Samples Treated With Sensodyne Toothpaste. *Note*. SEM: Scanning electron microscope

formation of apatite hydroxycarbonate crystals similar to the hydroxyapatite crystals found in the mineral composition of enamel. The deposition of calcium and phosphorus complexes and the release of these ions can start the remineralization process (20,23). Recently, dentists, considering the development of technology, have looked for natural and compatible products to prevent health problems. Several studies suggest that plants have different therapeutic properties such as antioxidant, anti-inflammatory, antiviral, antibacterial, antidiabetic, and anticarcinogenic effects. There are also limited studies that show the effects of plant extracts on caries-causing bacteria and remineralization. Recently, plant extracts have been employed as anti-microbial plaque agents in medicines to prevent tooth decay and reduce gingivitis. Furthermore, they have received special attention because they are non-chemical and non-synthetic. Further, these natural herbal products are safer and free of synthetic products' side effects. In addition, they are economically and locally available (24).

In this study, an oral environment with low salivary clearance was stimulated to create artificial primary caries-like lesions in enamel by reducing the concentration of calcium and phosphorus ions in the demineralization solution according to the pH cycle. This stimulation is highly similar to real-life natural conditions, leading to caries development and showing all the main histological aspects of natural caries (21,23). Additionally, in this study, the surface microhardness test was applied to measure the amount of remineralization of early enamel caries lesions. This evaluation quantitatively demonstrates minimal changes in the mineral content and is widely used in remineralization and demineralization studies. Measuring microhardness is a simple and reliable method to declare the changes made to the structure and mineral compounds of the tooth while indirectly indicating the extent of inorganic changes on the enamel of demineralized teeth (20). Moreover, the Vickers method was chosen in this study, which provides the possibility of accurate measurement and visual and numerical detection due to the shape of the pyramidal tooth transition (22). According to the results obtained in this study, all of the tested toothpastes increased the remineralization rate of primary enamel lesions. The amount of remineralization in primary enamel lesions in the group treated with Colgate toothpaste was lower than in the Sensodyne group and higher than in the Albodent group. Despite the difference in the amount of remineralization in

primary enamel lesions among the three groups treated with the three kinds of toothpaste used in the study, it was observed that all three groups were able to create more remineralization than the control group in primary enamel lesions. In the present study, the group treated with Sensodyne toothpaste showed the highest amount of microhardness and remineralization in the created primary enamel lesions compared to the other groups. This result is in agreement with the results obtained by Hsu et al and Abbasoglu et al (19,20). Considering that the concentration of fluoride in both kinds of toothpaste utilized in the current study was 1450 ppm, it seems that the higher ability of Sensodyne toothpaste to remineralize primary enamel lesions is due to the presence of NovaMin as a bioactive glass in the composition of this toothpaste. When NovaMin is exposed to saliva or water, an immediate reaction occurs that releases a vast amount of minerals such as calcium, silica, phosphorus, and sodium, which contribute to initiating the remineralization process (19). Furthermore, in another study that focused on the effect of NovaMin remineralization, Palaniswamy et al obtained the best results with toothpaste containing fluoride and NovaMin (Sensodyne Repair and Protect) (24). Mony et al also found that NovaMin is as effective as fluoride in improving the Ca/P ratio and hardening of demineralized enamel, which is in line with the results of the present study and confirms that NovaMin can be a new alternative for remineralization (25). In the study of Hsu et al, SEM images were used for the qualitative analysis of the surface, and it was observed that Sensodyne containing fluoride and NovaMin formed larger and more cohesive granules (honeycomb shape) in the intercrystalline seams compared to Sensodyne containing fluoride. It seems that the addition of NovaMin to toothpaste containing fluoride creates a synergistic effect, which conforms to the SEM results in the present study and another study (19). In the current study, microhardness was reported to be higher in the Sensodyne group containing NovaMin than the Colgate group containing only fluoride, which matches the results of the study conducted by Hsu et al. It seems that commercially available toothpaste containing NovaMin usually has fluoride as an additional component in its composition, although the amount of fluoride from sodium monofluorophosphate in NovaMin toothpaste is questionable. However, the fluoride of the toothpaste utilized on the teeth is probably washed away by the flow of saliva, and the sodium ions in NovaMin are replaced by hydrogen ions. Calcium and phosphorus are also released from NovaMin into the surrounding environment. With the temporary increase in pH, the calcium and phosphorus ions released from the Ca-P layer on the surface of the tooth crystallize into hydroxycarbonate apatite. In addition, fluoride is introduced into the bio-active glass (19). NovaMin seems to react with hydroxyapatite crystals and cause a change in morphology and increase in size, which probably minimizes the intercrystalline space and causes a faster remineralization process compared to fluoride alone (19). In the study of Narayana et al, comparing the effect of topical NovaMin remineralization with sodium fluoride gel on caries of permanent teeth, it was found that NovaMin toothpaste has a greater effect on the remineralization of caries-like lesions than fluoride, which corroborates the results of the present study (26). In addition, Mehta et al compared the remineralizing potential of toothpaste containing NovaMin and CCP-ACP and reported that NovaMin had a more successful effect on primary enamel caries repair (27).

Çelik et al also investigated the effect of the ginger plant extract, natural honey, and dark chocolate on the remineralization of primary enamel lesions and found that the mixture of these substances has a significant synergistic effect on preventing caries and increases the surface remineralization of the lesions, which is inconsistent with the results of the present study. This discrepancy can be due to the different ingredients used in Albodent herbal toothpaste. Further, in the above-mentioned study, hydroxyapatite discs were employed instead of teeth, and the microhardness measurement method was the Knoop method, which is different from the Vickers microhardness test. Moreover, honey and dark chocolate were utilized in the study of Çelik et al. Dark chocolate has the active ingredient theobromine, and many studies have shown its remineralizing and anti-caries properties. In addition, it seems that the effect of theobromine found in dark chocolate on enamel remineralization is greater than that of fluoride (21). In the study of Kiriştioğlu et al, the daily use of herbal toothpaste containing honey and ginger strengthened remineralization, which seems that the mineral content and antibacterial effect of ginger may have a role in the remineralization process, which was somehow consistent with the results obtained from the present study. According to our findings, the group treated with herbal toothpaste showed more remineralization and microhardness than the control group. Of course, the aforementioned study was conducted clinically. Furthermore, the number of samples was limited (15 patients), and white spot lesions were evaluated by fluorescence imaging (24). In the present study, SEM images were used to investigate morphological changes in the enamel surfaces of different groups. These images demonstrated that the demineralization process happened in the control group. These changes included the increase of surface porosity and slight etching, the increase of surface irregularities, and the creation of distinct and variable depressions. In the toothpaste group containing bioactive glass and fluoride (Sensodyne Repair), SEM images revealed the deposition of bioglass particles and the dispersion of particles on the enamel surface, as well as the covering of the irregularities created by bioactive glass deposits, which is in line with the results of the

study by Hsu et al (19), indicating that fluoride forms larger granules (honeycomb shapes) in the seams between enamel crystals. It is also in agreement with the findings of Burwell's study, showing that the combination of NovaMin with fluoride improves surface hardness after remineralization (29). In the SEM image of the herbal toothpaste group, we could not observe any granules, which was expected due to the lack of fluoride and bioactive glass, while we found hydroxyapatite crystals that were similar to the demineralized control group that was not treated with toothpaste.

Conclusion

The presence of NovaMin as a bioactive glass in the toothpaste composition along with fluoride can increase the efficiency of the toothpaste in the remineralization of primary enamel lesions and the microhardness of enamel compared to fluoride toothpaste without bioactive glass. Additionally, the effectiveness of herbal toothpaste, which does not contain essential artificial compounds, in the remineralization of primary enamel lesions and microhardness is less than that of synthetic toothpaste containing fluoride.

Authors' Contribution

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Visualization: Mohadese Shokripour.
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Writing–review & editing: Bahareh Asgartooran.

Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

The study protocol was approved by the Ethics Committee of Hamadan University of Medical Sciences (No. IR.UMSHA.REC.1401.009).

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