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ORIGINAL RESEARCH ARTICLE

Evaluation of pH and Calcium Ion Diffusion from Intra-canal MTA and Bioaggregate to Simulated External Resorption Cavities Through Dentinal Tubules

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Abstract

Purpose: The aim of the current in vitro study was to make a comparison among the effects of mineral trioxide aggregate (MTA), BioAggregate and calcium hydroxide on calcium and hydroxyl ion diffusion via dentinal tubules to the surfaces of the root in the absence of cementum in different root levels.
Materials and Methods: : The study consisted of 120 mature mandibular premolar teeth with a single root. The teeth were decoronated and instrumented using Protaper Universal rotary files. To simulate external root resorption, artificial defects were formed in the cervical-middle-apical thirds of the surfaces of the root. The teeth were grouped into four primary categories: Control (1), calcium hydroxide (2), MTA (3) and BioAggregate (4). The root canals of specimens from the control group remained unfilled. For specimens in the other groups, calcium hydroxide, MTA or BioAggregate were used to fill the root canals, respectively. Individual specimens were immersed in vials that contained 10 mL of distilled water. Measurements for the concentration of calcium and Ph were made at 1, 3, 7, 14, 21 and 28 days. Kruskal–Wallis H and Mann–Whitney-U tests were used to perform statistical analyses.
Results: According to the study findings, intra-canal placement of calcium hydroxide, MTA and BioAggregate caused calcium and hydroxyl ions to be diffused across the dentine. The outcomes revealed that the release of calcium and hydroxyl ions was greater in the calcium hydroxide groups compared to the MTA and BioAggregate groups ($p<0.05$). The properties of the MTA and BioAggregate groups were similar, and no differences were observed between them across the entire study period ($p>0.05$).
Conclusions: MTA and BioAggregate may be preferable for external root resorption cases due to their ability to stimulate the formation of hard tissue and release ions.

Key words: BioAggregate; Calcium hydroxide; External inflammatory root resorption; Ion diffusion; MTA

Introduction

External inflammatory resorption can occur when there is a root canal infection accompanied by external damage of the root surface following a traumatic event, such as avulsion or luxation. Also, the communication between peri-radicular tissues and the infected root canal system, by a lateral canal or apical foramen, may induce the external inflammatory resorption where the inflammatory response is induced by the bacteria and/or their byproducts.[1] The infection of the root canal system should be eliminated to enable the inflammation to be discontinued and the clastic cells deactivated; thus, the resorption of the root can be interrupted and adjacent bone tissue may be recovered.[2]

To date, calcium hydroxide or different biomaterials that facilitate depositing a hard tissue barrier while offering a biologic seal have been the mainstay treatment regimens for external root resorption to induce healing or repair in root resorption defects.[3] To eliminate the infection and terminate the process of resorption, ready-to-use calcium hydroxide pastes are widely employed in endodontic therapy. Previous research has established that long-term intracanal calcium hydroxide medication significantly increases the calcium ion level on the external surface of the root in addition

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to the rise of the pH value of dentin tissue.[4] However, there are several drawbacks associated with long-term calcium hydroxide medication even if the external inflammatory root resorption can be effectively treated. Many visits spanning an extended time period are required for the treatment, along with patient participation and cooperation.[5] Additionally, it has been proposed that when used in the long term, calcium hydroxide may weaken dentinal structures, thus causing the mechanical properties of radicular dentine to be reduced and fracture resistance to be decreased.[6] Furthermore, although the complete removal of calcium hydroxide is necessary prior to the root canal system being filled, it is virtually impossible to remove the remnants of calcium hydroxide from the irregular canal walls.[7]

Various calcium silicate-based endodontic bioactive materials have been developed for usage in vital and non-vital pulp therapies, including root canal infection related external inflammatory resorptions to overcome these challenges. Thus, calcium silicate-based cements like mineral trioxide aggregate (MTA), BioAggregate etc. have begun to be used instead of calcium hydroxide for treating several pulpal and periodontal healing concerns subsequent to dental trauma during the past 30 years. Numerous studies have demonstrated favorable biological responses to these materials owing to their effect on the formation of hard tissue as a result of their ability to release calcium and hydroxyl ions.[8–10]

Since calcium silicate-based cements are recommended for use as orthograde root canal filling materials, it may be beneficial to use them in cases of traumatic injury without long-term calcium hydroxide medication, depending on whether they have adequate ion release capacity over time.[11] Thus, the current in vitro study was aimed at assessing the calcium and hydroxyl ion diffusion capacities of MTA and BioAggregate via dentinal tubules to the surfaces of the root in the absence of cementum at different root levels in comparison with calcium hydroxide paste.

Material and Methods

The local ethics committee of the University provided approval to conduct the study (Approval No: YDU 11/3-8). One hundred twenty non-carious permanent single-rooted mandibular premolar teeth with mature root formation were gathered and kept in physiologic saline solution prior to the experiment. To assess the root size and canal morphology, radiographs were taken. Teeth with more than a single root canal, previous endodontic treatment, external/internal resorption, inadequate root development, or root crack/fracture were excluded from the study. Teeth with identical root form and root canal dimensions were collected together and randomly assigned to one of the experimental groups.

Tooth crowns were removed using a slow-speed diamond disk and the working length was determined visually by placing #10 K-file into the canal until it could be observed at the apex, then withdrawing it by 1 mm. Instrumentation of each root canal was performed with a Protaper Universal System (Dentsply Maillefer, Ballaigues, Switzerland) up to F5 in the sequence in line with the manufacturer's recommendations. Irrigation procedures were performed using 5 mL 5.25% NaOCl (Wizard, Rehber Kimya San., Turkiye) with a 27-gauge needle at each file.

Standardized cavities were formed in the cervical, middle and apical third regions of the roots' buccal surfaces using an ISO No:16 cylindrical diamond fissure bur (Hager & Meisinger GmbH, Neuss, Germany) to mimic external root resorption in tooth roots. This procedure was carried out gradually in 2-3 steps, using a parallel technique with a digital radiography device and making measurements on the image each time, to standardize the remaining dentin thickness as much as possible. For the calibration of the measurements on radiography, Protaper Universal Sx file (19 mm in length) was used as a reference. By using the imaging software (Planmeca Dimaxis Pro Version 4.3.2.), the thickness of the remaining dentine was used as the measurement of the shortest distance from 3 different regions of the created cavity to the root canal. The average of 3 measurements was recorded as the thickness of the remaining denting for the relevant tooth. This process continued until a dentin thickness of between 0.75 and 0.9 mm was obtained in the prepared cavities. Teeth with dentin thickness below this range were not included in the study. Resultantly, the mean residual dentin thickness for all teeth was 0.84 mm ($\pm$ 0.07).

To remove the smear layer, irrigation of the root canals and resorption cavities was performed using 5 mL 17% EDTA (Ultradent® EDTA, 65 Ultradent Products Inc., USA), 5 mL 5% NaOCl (Wizard, Directory Kimya San., Turkey) and 10 mL of distilled water, respectively. Then, paper points were used to dry the canals and samples were separated equally into four main groups based on the filling material used and subgroups of each of the primary groups were also created based on the location of the simulated resorption cavity as follows:

Group 1 (Control, n = 30): The root canals remained empty to act as controls. The locations of the simulated resorption cavities were in the coronal third (Group 1a, n = 10), middle third (Group 1b, n = 10) and apical third (Group 1c, n = 10) parts of the roots.
Group 2 (CH, n = 30): Calcium hydroxide paste was used for filling the root canals (Calcipast, Cerkamed Medical Co, Poland). The locations of the simulated resorption cavities were in the coronal third (Group 2a, n = 10), middle third (Group 2b, n = 10) and apical third (Group 2c, n = 10) parts of the roots.
Group 3 (MTA): MTA was used to fill the root canals (ProRoot® MTA, Dentsply Tulsa Dental Specialties, USA). The locations of the simulated resorption cavities were in the coronal third (Group 3a, n = 10), middle third (Group 3b, n = 10) and apical third (Group 3c, n = 10) parts of the roots.
Group 4 (BioAggregate): The root canals were filled with BioAggregate (Innovative BioCeramix Inc., Vancouver, BC, Canada). The locations of the simulated resorption cavities were in the coronal third (Group 4a, n = 10), middle third (Group 4b, n = 10) and apical third (Group 4c, n = 10) parts of the roots.

The preparation of all materials was conducted in accordance with the manufacturer's guidelines. In Group 3 and Group 4, mixed MTA and BioAggregate were delivered into the root canal space incrementally with a carrier and then condensed with hand pluggers. Sealing of the coronal accesses was achieved using IRM (Intermediate Restorative Material, Dentsply Caulk, USA) in all groups. Radiographs were made to examine the density of the filling in Groups 2, 3 and 4. Two coats of nail polish and then wax were administered to isolate the sample surfaces, leaving only the resorption cavities exposed (Figure 1). Subsequently, all samples were immersed in individual plastic vials that contained 10 mL of deionized water, and kept at 37°C with 100% humidity. pH values of the immersion media were determined with a pH meter (S20 SevenEasy™, Mettler Toledo, USA). The pH of the medium was measured 3 times for each sample and the mean value was recorded. An atomic absorption spectrophotometer was used to measure the calcium concentrations of the immersion media (iCE 3500 AA Spectrometer, Thermo Scientific, USA). Measurements were made on days 1, 3, 7, 14, 21 and 28.

Statistical analysis of the data was conducted using SPSS 22.0 software (IBM SPSS Statistics, New York, USA). The non-parametric Kruskal–Wallis H test was used to statistically analyze the data, and a significance level of 0.05 was accepted. The Mann-Whitney U test with Bonferroni correction was utilized in the case of significance with the Kruskal-Wallis test.

Results

Calcium ion concentration in all experimental groups throughout the study is presented in Table 1. The calcium hydroxide sub groups

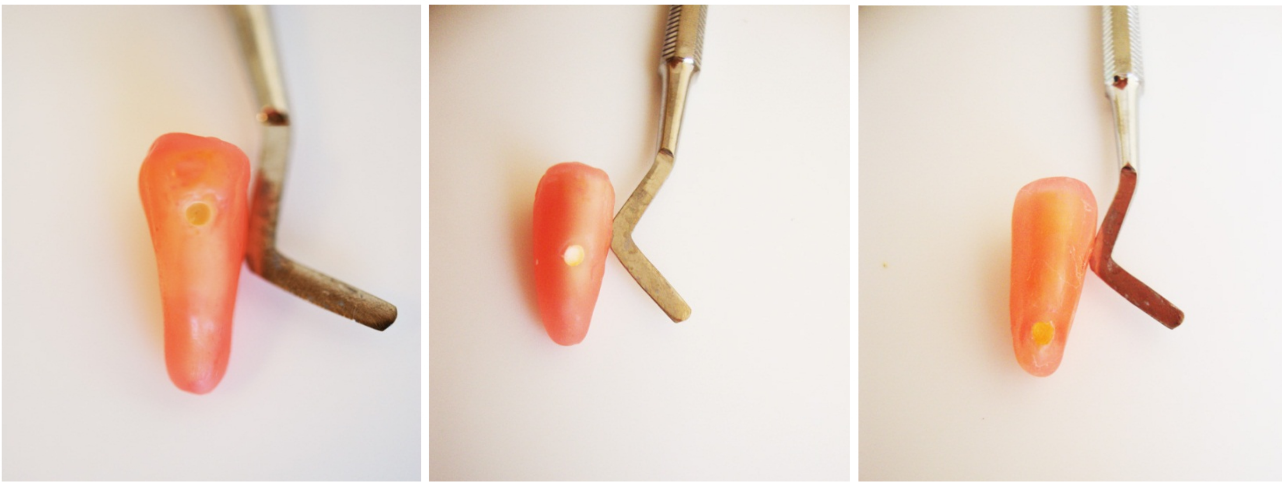

Figure 1. Specimens in which artificial resorption cavities were opened in the cervical third, middle third and apical third regions and isolated with nail polish and wax.

Table 1. Table 1. Calcium ion concentration (ppm) in all experimental groups throughout the study

Study Groups	Day 1 Mean (± SD)	Day 3 Mean (± SD)	Day 7 Mean (± SD)	Day 14 Mean (± SD)	Day 21 Mean (± SD)	Day 28 Mean (± SD)
Coronal Groups						
1a. Control	0.451 a (± 0.131)	1.232 a (± 0.313)	1.572 a (± 0.276)	2.095 a (± 0.365)	3.147 a (± 0.591)	4.016 a (± 0.892)
2a. CH	0.869 b (± 0.229)	2.693 b (± 0.699)	7.137 b (± 1.985)	16.196 b (± 2.645)	19.686 b (± 2.362)	23.307 b (± 2.298)
3a. MTA	0.51 a (± 0.302)	1.75 a (± 0.588)	2.207 a (± 1.043)	4.018 c (± 1.53)	5.188 c (± 1.974)	7.554 c (± 2.704)
4a. BioAggregate	0.66 b (± 0.209)	2.013 c (± 0.853)	2.739 c (± 0.96)	5.216 d (± 1.489)	6.294 c (± 1.499)	8.464 c (± 1.973)
Middle Groups						
1b. Control	0.294 a (± 0.048)	0.931 a (± 0.323)	1.238 a (± 0.317)	1.642 a (± 0.327)	2.251 a (± 0.397)	2.872 a (± 0.555)
2b. CH	0.444 b (± 0.091)	2.261 b (± 0.67)	5.693 b (± 1.391)	12.974 b (± 2.915)	14.477 b (± 3.285)	16.85 b (± 3.051)
3b. MTA	0.275 a (± 0.034)	1.301 a (± 0.284)	1.595 a (± 0.288)	2.098 c (± 0.676)	2.752 c (± 0.872)	3.899 c (± 1.211)
4b. BioAggregate	0.32 a (± 0.076)	1.142 a (± 0.449)	1.404 a (± 0.428)	2.103 c (± 0.315)	2.803 c (± 0.296)	4.149 c (± 0.355)
Apical Groups						
1c. Control	0.216 a (± 0.062)	0.862 a (± 0.255)	1.058 a (± 0.21)	1.442 a (± 0.25)	1.946 a (± 0.359)	2.344 a (± 0.479)
2c. CH	0.392 b (± 0.193)	2.077 b (± 0.85)	3.28 b (± 1.122)	8.358 b (± 2.181)	9.306 b (± 2.138)	11.966 b (± 2.631)
3c. MTA	0.307 b (± 0.143)	1.118 a (± 0.39)	1.36 a (± 0.378)	2.249 c (± 0.553)	2.837 c (± 0.712)	3.478 c (± 1.075)
4c. BioAggregate	0.275 b (± 0.108)	1.11 a (± 0.419)	1.358 a (± 0.501)	1.978 c (± 0.724)	2.658 c (± 0.803)	3.475 c (± 1.116)

Sharing same letter in the columns of coronal, middle and apical study groups indicate the absence of statistically significant differences among the groups (p>0.05). SD= Standart deviation

exhibited the highest calcium values (Group 2a, 2b and 2c) on all days of measurement starting from day 1 ($p<0.05$). Figure 2 shows the day-by-day calcium ion release results of the main study groups. The calcium ion diffusion level of Calcium Hydroxide main group (Group 2) was statistically higher than other study groups ($p<0.05$) while no differences were detected between the MTA (Group 3) and BioAggregate (Group 4) main groups ($p>0.05$). The calcium ion concentrations were significantly lower ($p<0.05$) than those of others in the study period.

The pH values of all sub groups and the main groups are shown in Figure 3 and Table 2. When the mean pH values of the groups over the whole measurement period were compared, no statistically significant differences between the MTA and BioAggregate groups were observed, while the control group had statistically significantly lower pH values compared to the other three groups. The calcium hydroxide group exhibited significantly higher pH values compared to the MTA and BioAggregate groups.

Figure 4 presents the mean calcium ion diffusion levels of the coronal, middle and apical third subgroups. The coronal, middle

Table 2. Mean and Standard Deviation of pH values of the main groups.

Main Groups	Day 1 Mean (± SD)	Day 3 Mean (± SD)	Day 7 Mean (± SD)	Day 14 Mean (± SD)	Day 21 Mean (± SD)	Day 28 Mean (± SD)
1. Control	7.11 a (± 0.2)	7.28 a (± 0.1)	7.22 a (± 0.1)	7.01 a (± 0.1)	7.11 a (± 0.2)	6.76 a (± 0.3)
2. CH	7.28 b (± 0.1)	7.3 a (± 0.1)	7.26 a (± 0.2)	7.28 b (± 0.2)	7.59 b (± 0.3)	7.2 b (± 0.3)
3. MTA	7.15 a (± 0.2)	7.31 a (± 0.1)	7.26 a (± 0.1)	7.09 a (± 0.1)	7.39 c (± 0.2)	7.07 b (± 0.2)
4. BioAggregate	7.22 ab (± 0.1)	7.32 a (± 0.1)	7.24 a (± 0.1)	7.07 a (± 0.1)	7.39 c (± 0.3)	6.87 c (± 0.3)

Means within a column sharing the same letter are not significantly different (p>0.05). SD= standart deviation

and apical third subgroups demonstrated statistically significant differences from each other. The highest calcium ion diffusion levels were detected in the coronal group, while the lowest levels were detected in the apical group ($p<0.05$). The same findings were also identified for the pH measurements. The coronal group exhibited the highest pH values, whereas the apical group demonstrated the lowest ($p<0.05$).

Discussion

Along with the deterioration of the continuity of the layer of cementum on the surface of the root, the development of intra-canal infection is generally a trauma sequela and triggers a process called external inflammatory root resorption, which can cause the loss of the tooth.[12] The main purpose of the treatment to be applied is to prevent osteoclastic activity on the surface of the root by starting endodontic treatment before the tooth becomes infected.[13] The International Association of Dental Traumatology guidelines recommend calcium hydroxide as an intra-canal medicament for up to 1 month in avulsion cases.[14] Calcium hydroxide shows its biological and antibacterial activity in the root canal by chemically dissociating into calcium and hydroxyl ions and the effect of these ions on bacteria and tissues.[15] The dissociated hydroxyl ions cause the pH to rise. With elevated pH, protein denaturation occurs, bacterial DNA and membranes are damaged and lose their vitality, and lipopolysaccharides, a toxin produced by gram-negative bacteria, are inactivated.[16] The alkaline environment formed by hydroxyl ions reaching the periodontal tissues suppresses the osteoclastic activity in the region and supports healing by creating suitable conditions for hard tissue formation.[17] Another effect of high pH is to activate the alkaline phosphatase enzyme, which is acknowledged to have a close association with the process of mineralization.

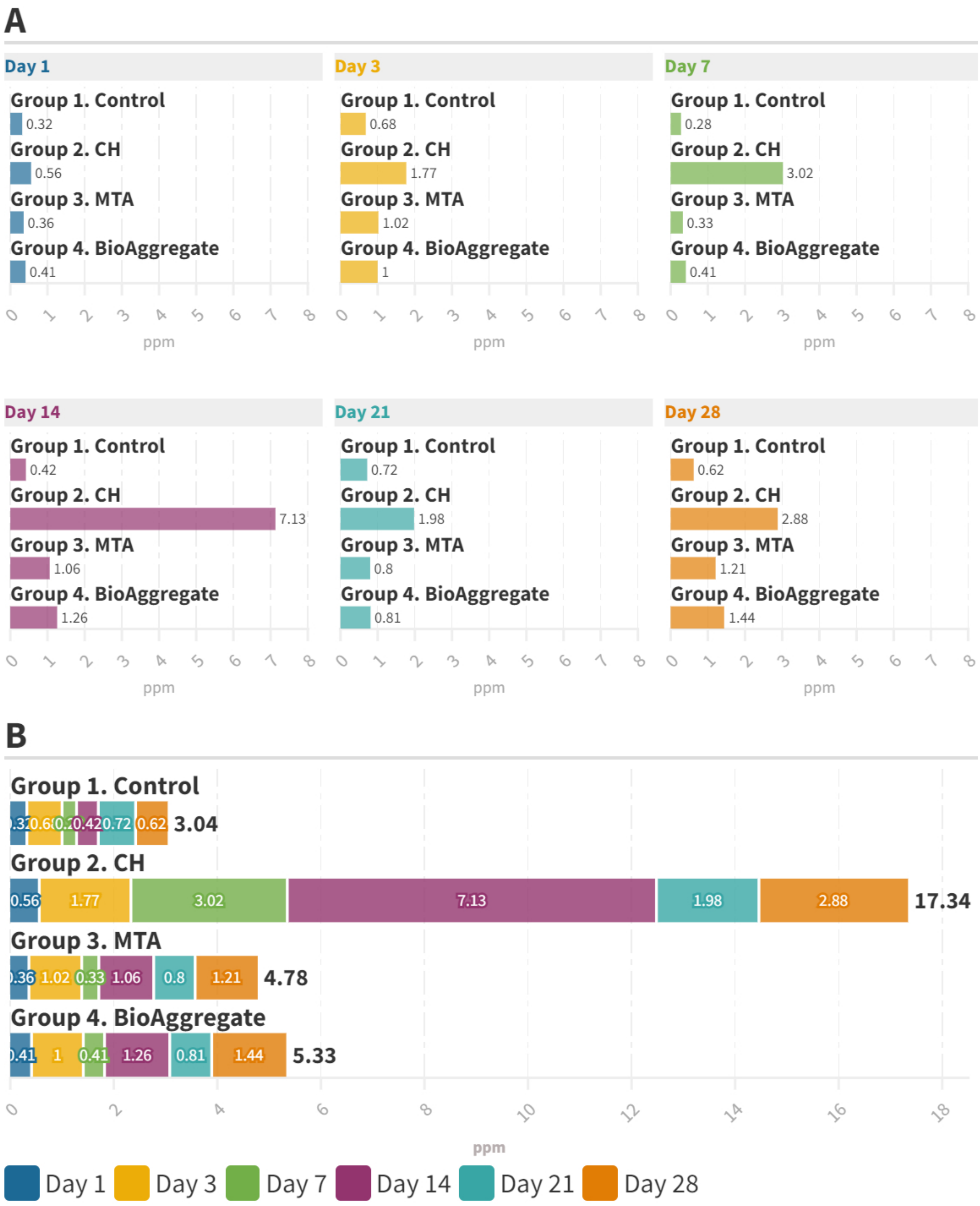

Figure 2. A. Day by day calcium ion diffusion levels of the main groups. **B**. Cumulative values of calcium ion diffusion rates of the main groups.

Another effect of high pH is to activate the alkaline phosphatase enzyme, which is known to be closely related to the mineralization process by enhancing the hard tissue formation. Alkaline phosphatase enables the removal of phosphate groups from various molecules attached to the tissues. The liberated phosphate ions react with calcium ions from the bloodstream, which forms calcium phosphate precipitates in the organic matrix. Calcium phosphate is the molecular structural unit of hydroxyapatite.[15] It has also been reported that the amount of calcium present in the resorption site controls the activity of osteoclasts.[18] Additionally, as calcium is slowly released, it stimulates the growth factors and upregulates fibronectin gene expression, which are necessary for the formation of hard tissue.[19,20]

Various studies have reported that calcium and hydroxyl ions dissociated from calcium hydroxide placed in the canal can diffuse into the dentin and access the surface of the root.[21] However, other

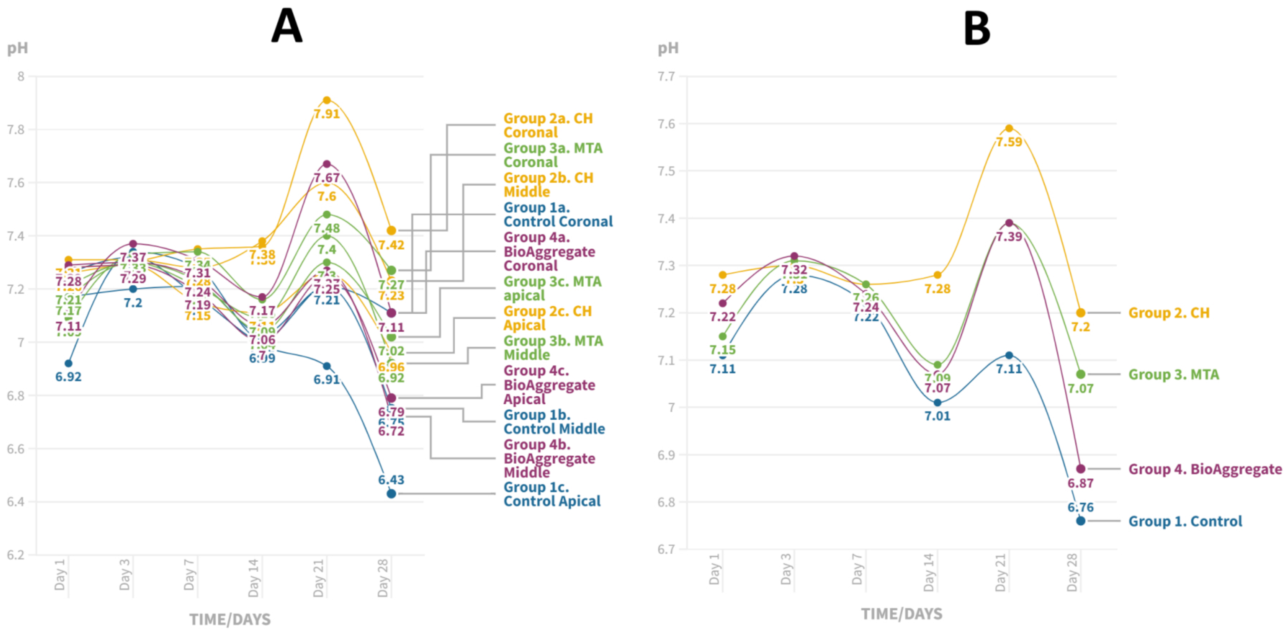

Figure 3. **A**. The pH values of all sub groups at various time intervals **B**. The pH values of the main groups at various time intervals.

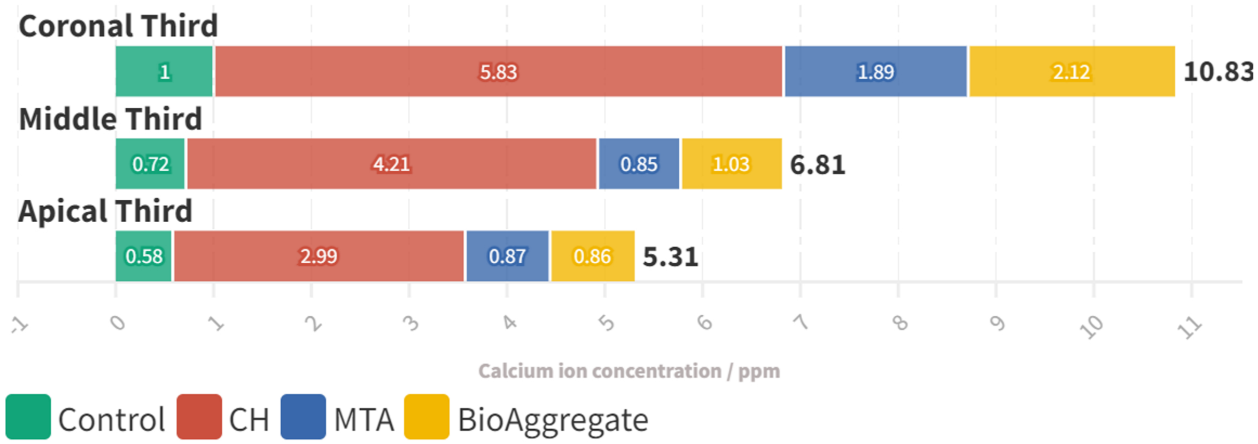

Figure 4. The mean calcium ion diffusion levels of coronal, middle and apical third subgroups.

studies have reported that calcium ions can reach the root surface, whereas hydroxyl ions are reported to be buffered in the dentinal tubules and are therefore unable to do so.[3,22] Our results showed that calcium and hydroxyl ions, originated from intra-canal calcium hydroxide, MTA and Bioaggregate, can reach the cementum-free root surfaces by passing the dentin barrier, which is approximately 0.84 mm thick. The orientation of the dentinal tubules is a factor that can affect ion diffusion.[3] In the root's middle third, the tubules extend at an angle of 90° in the resorption area, while in the apical region they follow a more oblique path. This increases the distance the ions have to travel. As far as we know, there have been no controlled studies comparing the differences of calcium or hydroxyl ion diffusion rates in different regions of the root. Therefore, in our study, resorption cavities were formed in three different regions of surfaces of the root. Another issue that may affect ion diffusion is the varying diameter and amount of dentinal tubules in distinct areas of the root. It has been reported in various studies that all these factors affect the diffusion of hydroxyl ions released from calcium hydroxide.[22] However, the remaining dentin thicknesses have not been considered in many studies.[21,23,24] Accordingly, in the present study, preparation of the samples was conducted such that they had a standardized remaining dentin thickness of 0.84 mm, which was confirmed by radiological imaging. A similar methodology was also used by some previous studies.[3,4,25] Another factor that can affect ion diffusion from the dentinal tubules is the age of the patients. However, due to the difficulty in obtaining the extracted teeth we used in the study and the lack of records of the ages of the patients whose teeth were extracted, this factor was ignored in our study by not making any age-related standardization, and it can be considered as the main limitation of the current study.

Regarding the calcium values of the present study, the calcium ion concentrations in the cervical, middle and apical third resorption cavity groups containing calcium hydroxide were determined to be significantly higher compared with the control groups on all days of measurement ($p<0.05$). This result is in agreement with the findings of past studies.[26−28] In the literature, calcium ion releases of MTA and bioceramic materials in liquid media have been investigated in various studies. Fridland and Rosado investigated the solubility of ProRoot MTA and reported that the main compound that dissociated from MTA in liquid medium was calcium in the form of hydroxide.[29] De Vasconcelos et al. studied the calcium ion releases of MTA-based materials and reported that calcium ions were regularly released from the different types of MTA during the 168-hour working period.[30] Similar results were presented by other researchers.[31–33] There are relatively few studies on calcium ion diffusion from root dentin of MTA or MTA-based materials. In the study performed by Özdemir et al.[3], the findings showed that the calcium concentration levels of samples in the Pro-Root MTA group were significantly higher compared to the control group on all days (1, 3, 7, 14, 28th days) of measurement, which concurs with the findings obtained by George et al.[25] In both studies, Pro-Root MTA was found to be more successful than the current study when the first two-week measurements were evaluated, although the average residual dentin thickness reported in these studies was approximately 1.7 times higher than in our study. The explanation for this result could be that the surface area differences of the formed resorption cavities. The diameter of the bur 016 that we created in our study, and therefore the diameter of the cavities, was 1.6 mm. Özdemir et al.[3] and George et al.[25] created resorption cavities with a diameter of 3 mm in their studies. This difference, which is approximately 1.8 times, increases to approximately 3.5 times when the surface area is calculated. In other words, the surface area of the cavities created in the other two studies was 3.5 times larger than the ones created in the current study. The higher volume of calcium ions that will reach the solution from the samples with larger surface area may create a statistically significant difference to the control group on the days of measurements, and this situation is demonstrated in the results.

A statistically significantly higher concentration of calcium was detected in the cervical group containing BioAggregate compared to the control group in all evaluation periods. Thus, BioAggregate appears to be more successful than MTA in the cervical third region of the root. In the middle and apical groups containing BioAggregate, similar to the MTA groups, higher results were obtained in all periods compared to the control group, although these results were statistically significant on the 14th day and after. In the literature review, no study has been found regarding BioAggregate material to compare the present results. Several investigations have shown that hydroxyl ions are diffused from intra-canal calcium hydroxide to simulated external root defects.[23,34,35] Nerwich et al. reported that while diffusion of the hydroxyl ions released from the calcium hydroxide inserted into the root canal to the dentin can occur within hours, it can take from 1 to 7 days for it to reach the root's external surface.[34] Chamberlain et al. created resorption cavities at a distance of 1 mm, 3 mm and 5 mm from the root apex and investigated the pH change caused by placing calcium hydroxide in the canal at different levels at various periods.[21] They concluded that placing calcium hydroxide in the root canal causes hydroxyl ions to be diffused from the dentinal tubules to the surface of the root and the extent to which this occurs depends on the amount of calcium hydroxide within the root canal.[21] These results are consistent with our findings on hydroxyl ion diffusion from calcium hydroxide. However, there is no consensus within the literature on the diffusion of hydroxyl ion from MTA. In the study conducted by Özdemir et al., it was concluded that MTA placed in the root canal did not produce any changes in the pH of the immersion media.[3] Considering this result, they reported that it should not be expected to aid with the healing caused by the high pH that will occur on the root surface when orthograde MTA is used in the canal.[3] On the other hand, Heward and Sedgley used MTA and calcium hydroxide in their study and found that hydroxyl ion diffusion occurred in both groups and that MTA was more successful in this regard.[13] According to the findings of the current study, it can be thought that hydroxyl ions dissociated from calcium hydroxide placed in the root canal can reach the resorption cavity at all root levels, however only on the 14th day and after, can be effective by showing continuity. In contrast to the calcium hydroxide group, MTA and BioAggregate demonstrated a statistically significant difference on the 21st day compared to the control group.

In our study, calcium ion diffusions from dentinal tubules differed at different root levels. These findings concur with those of past studies that have investigated the dentin diffusion of hydroxyl ions.[23,34,36] These results are likely to be related to the increase in the diameter and amount of dentinal tubules from the apical to the cervical of the root in addition to the increase in dentin permeability. Another factor explaining this result could be that the smear layer in the apical region was not sufficiently removed.[37]

Conclusion

Calcium hydroxide exhibited superior properties compared to MTA and BioAggregate regarding calcium and hydroxyl ion diffusions. MTA and BioAggregate materials showed similar properties and did not show superiority over each other during the entire study period. Although the MTA and BioAggregate materials showed slower and lower amounts of calcium and hydroxyl ion diffusions in the 28-day working period, this may be advantageous for the materials as they may have a slow and sustainable release of ions across extended periods.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by U.A. and K.P. The first draft of the manuscript was written by U.A. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

Authors declare that they have no conflict of interest.

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