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# Comparison of Pulpal Response Following Direct Pulp Capping Using MTA and Zinc-doped Bioglass

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## ABSTRACT

**Background and Objective:** Management of deep caries and pulp exposures depends on the severity of the disease. The rapid development of preventive materials and techniques has significantly influenced restorative treatment methods. Therefore, the aim of this study is to produce and evaluate a type of bioactive glass containing Zn (Zn-BAG= Zinc-doped Bioglass) and to investigate its performance on the pulp and the formation of dental bridges following direct pulp capping in comparison to the standard gold material MTA (Mineral Trioxide Aggregate).

**Methods:** The conventional sol-gel method synthesized bioglass 45S5 with 2%mol zinc. In this experimental animal study, 10 maxillary first molars of 10 Wistar rats were subjected to direct pulp capping and divided into two groups of five according to the materials used: group 1 (DPC [Direct pulp cap] + MTA) and group 2 (DPC + Zn-BAG). After 8 weeks of direct pulp capping, the rats were sacrificed, and teeth were sectioned and prepared for histological analysis. The degree of inflammatory pulpal response (no inflammation, mild inflammation, moderate inflammation, severe inflammation, necrosis), location of a dentin bridge (at the site of pulp exposure, not adjacent to the site of exposure, and combination), percentage of dentin bridge formation (%) (25%>, 25%-50%, 50%-75%), and the quality of dentin bridge formation (without tubules, irregular tubular pattern, regular tubular pattern) were analyzed and scored.

**Findings:** In the electron microscope view, Zn-BAG particles exhibited a plate-like shape with less than 100 nm particle size. The EDS analysis confirmed the presence of zinc in the Bioglass structure. There was no significant difference between the type of pulp capping agent and the degree of inflammatory pulpal response, location of a dentin bridge, percentage of dentin bridge formation, and the quality of dentin bridge formation.

**Conclusion:** Zn-BAG and MTA pulp capping materials showed similar desirable cellular and inflammatory responses over pulpal exposure. Zn-BAG is a promising candidate for pulp capping material.

**Keywords:** *Dental Pulp Capping, Mineral Trioxide Aggregate, Bioglass.*

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## Introduction

Preservation of pulp vitality is the major concern of restorative dentistry (1). Dental pulp is a unique vascularized connective tissue. Like other connective tissues, the dental pulp has the potential for self-renewal and recovery as a response to external stimuli (2). Vital pulp therapy is designed to eradicate bacteria from the dentin-pulp complex and preserve healthy pulp that has been exposed to external stimuli (trauma and caries) (3).

Management of deep caries and pulpal exposure depends on the severity of the disease. Management of deep caries lesions with a normal pulp or reversible pulpitis in deciduous teeth plays a critical role in maintaining proper oral health (4). The rapid development of dental materials and preventive techniques has significantly changed the professional approach to restorative dentistry. Biological, non-invasive, or minimally invasive methods have gained popularity over conventional treatments (5).

Three well-known pulp treatment methods include: pulpotomy, pulpectomy, and direct pulp capping therapy (vital pulp exposure) (6). Direct pulp capping (DPC) is a less invasive vital pulp therapy designed to maintain the integrity of pulpal tissue (2). Pulp capping aims to improve the healing of vital pulp exposure using biocompatible materials. Pulp capping materials must have the ideal properties to balance inflammation and pulp regeneration (7). An ideal pulp-capping material should be biocompatible, easy to use, establish a good seal to prevent bacterial leakage, facilitate dentine remineralization, and stimulate reparative dentin bridge formation (8-12).

Mineral trioxide aggregate (MTA) was introduced in 1995 by Torabinejad as a retro filling material in endodontic treatments. MTA exhibits satisfactory properties such as high biocompatibility, good sealing ability, high alkalinity, gradual release of calcium, and stimulation of cytokine release. Mineral trioxide aggregate is also an ideal material for direct pulp capping. MTA has the potential to improve cell proliferation rate and create a homogeneous calcified bridge beneath the exposed pulp tissue (2). However, MTA has some limitations, such as cytotoxicity in the initial setting stage, long setting time, high cost, difficult handling and the need to provide adequate moisture during setting. Therefore, the development of a new generation of direct pulp capping (DPC) biomaterials is necessary for regeneration of the dentine-pulp complex (13-15).

Bioactive glass (BAG) is a bioceramic that exhibits innovative bioactive properties for the replacement, regeneration and repairing of hard tissues, including bone and teeth (13). The apatite-forming mechanism and biomineralization ability of bioactive glass-based materials to induce hard tissue (i.e., bone, enamel, dentin, and cementum) formation have been recognized (16).

Initially, BAG was introduced as Bioglass® 45S5 with 45% $SiO_2$, 24.5% CaO, 24.5% $Na_2O$, 6% $P_2O_5$ (16). Bioactive glass exhibits good antibacterial properties and promotes proliferation, differentiation, and mineralization of human dental pulp cells (14). Bioactive glass is biocompatible, releases therapeutic ions, and forms a hydroxyapatite (17). Another advantage of the BAG is the likelihood of integrating specific ions within its construction throughout sol-gel (wet chemical technique) preparation. Different therapeutic ions such as Co, Zn, Cu, Sr, Mg, Ag, and Ce, have been added to bioactive glass to enhance biological activity towards precise biological responses (18-20). An in vitro study suggested that the ions released by the sol-gel bioactive glass nanoparticles had a high density of mineralized nodules but did not prevent the progress of human dental pulp stem cells. Sol-gel-derived bioactive glasses following direct pulp capping inspired the development of a dense dentinal bridge with inflammatory reactions like mineral trioxide aggregate (10).

Zinc (Zn) is widely used in dental materials due to its bacteriostatic and cariostatic properties. Several zinc-based dental materials have been introduced, including zinc phosphate (ZP), zinc oxide eugenol (ZOE),

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and zinc polycarboxylate (ZPC) (17). Zinc has been shown to stimulate the glasses structure's bioactivity, biocompatibility, and antimicrobial properties. Appropriate doses of zinc supplements can increase the alkaline phosphatase activity and DNA content in bone tissues (21, 22). A study by Oh et al. showed that zinc-added sol-gel bioactive glass granules stimulated the growth and osteogenic differentiation of mesenchymal stem cells (MSCs) (23). Zinc doped Bioactive glass (Zn-BAG) 5% caused changes in the morphology of endothelial cells by structural rearrangement that led to the formation of capillary-like networks in HUVECs (Human Umbilical Vein Endothelial Cells) (18). An et al. suggested that in the concentration range from $3\times10^{-5}$ to $8\times10^{-5}$ M, extracellular $Zn^{+2}$ could enhance cell viability, migration, expression levels of osteogenic differentiation, and zinc transporters genes in human dental pulp cells (hDPCs). Optimal zinc supplementation can be incorporated into pulp capping agents and controlled release to improve clinical outcomes (11).

The aim of this study is to construct and evaluate the efficacy of zinc-doped bioactive glass (Zn-BAG) on the histological pulp response and dentin bridge formation following direct pulp capping compared to mineral trioxide aggregate (MTA), a gold standard material.

## Methods

**Synthesis and characterization of Bioglass containing zinc (Zn-BAG):**

**Materials:** The chemical materials include Zinc Nitrate ($ZnNO_3$), Nitric acid ($HNO_3$), Tetraethyl Orthosilicate (TEOS), Triethyl Phosphate (TEP), Ca $(NO_3)_2(4H_2O)$, and Sodium Nitrate ($NaNO_3$) were all obtained from Sigma-Aldrich (Germany).

**Synthesis:** Bioglass 45S5 with 2 mol% zinc was synthesized by the conventional sol-gel method. Zinc Nitrate was used as a zinc source. To synthesize bioactive glass (0.1 mol), 12 mL of 1 normal nitric acid was prepared and 7.5 g of TEOS was dissolved in the nitric acid solution. The solution was stirred for 50 min to ensure the hydrolysis of the solution. Then, with a 45-minute interval, 2.26 g of TEP, 6.94 g of 4-aqueous calcium nitrate, 4.54 g of NaNO3, and 0.522 g of zinc nitrate were added simultaneously. It took 30 minutes to complete the reaction. Then, the solution was exposed to room temperature for the aging process for 72 hours and then dried at 100 ˚C for 24 hours. The resulting bioglass powder was sintered at 740 ˚C for 6 h with a maximum ramp rate of ≈ 5°C/minute. The synthesized Bioglass was analyzed using X-ray diffraction (Seifert XRD 3003 PTS) and infrared spectroscopy (Fourier Transform, FTIR; Nexus 870). Finally, the morphology and percentages of element composition of produced powder were analyzed using chemical microanalysis techniques (scanning electron microscopy (SEM) and energy dispersive X-Ray spectroscopy (EDS).

**Direct Pulp capping:** After being approved by the Ethics Committee of Jundishapur University of Medical Sciences in Ahvaz with the code IR.AJUMS.ABHC.REC.1400.016, the present experimental animal study was conducted on 10 male albino Wistar rats. Ten maxillary first molars of 10 Wistar rats were subjected to direct pulp capping (DPC) and divided into two groups of five according to the materials used: group 1 (DPC+MTA) and group 2 (DPC+Zn-BAG). The rats were first anesthetized with a mixture of ketamine 10% (1 ml) and Xylazine 2% (0.2 ml) (Alfasan Co., Netherlands). A volume of 3.8 ml of isotonic saline was added to the mixture, and 0.2 ml of the solution was injected into the peritoneum site at a dosage of 500 g/body weight. The oral cavity was then mechanically prepared and cleaned using a small brush and sodium hypochlorite solution and then disinfected with chlorhexidine digluconate. The enamel-dentine was excavated under 4.5 magnification using loupes (Germany Heine®) and cylindrical bur (Tizkavan, Tehran, Iran). The pulp was exposed by diffusing through the remaining dentine of the cavity floor using a periodontal explorer following access to the pulp cavity; the dental cavity was thoroughly rinsed with sterile

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normal saline. After hemostasis achievement with a sterile paper point, the exposed pulp was capped according to the table of random allocation and the mentioned groups. In group 1, ProRoot MTA cement (DENTSPLY, USA), and in group 2, synthesized Zn-BAG were used. The teeth were restored with light-cure glass ionomer cement (GC Company, Tokyo, Japan). To minimize occlusal forces and stress, the cusp of opposing teeth was reduced.

**Histological analysis:** The rats were sacrificed after 8 weeks of direct pulp capping. The right halves of the maxilla were sectioned and fixed in a solution of 2.5% glutaraldehyde and 10% formalin (Wako, Osaka, Japan) for a week. The samples were decalcified in 14% ethylenediaminetetraacetic acid (EDTA) for 14 days. The samples were embedded in paraffin. The paraffin-embedded blocks were cut into 5 µm sections. The sections were stained with hematoxylin-eosin (H&E). Specimens were examined using a light microscope (Olympus Corporation, Tokyo, Japan).

For each sample, the degree of inflammatory pulpal response (no inflammation, mild inflammation, moderate inflammation, severe inflammation, necrosis), location of dentin bridge (at the site of pulp exposure, not adjacent to the site of exposure, and combination), percentage of dentin bridge formation (%) (25%>, 25%-50%, 50%-75%), and the quality of dentin bridge formation (without tubules, irregular tubular pattern, regular tubular pattern) were analyzed and scored (24).

Data were analyzed using SPSS version 21 software and chi-square test, and $p<0.05$ was considered significant.

## Results

**Characterization of Bioglass containing zinc (Zn-BAG):** Bioglass systems containing $SiO_2$ - CaO - $Na_2O$ - $P_2O_5$ tended to form a sodium-calcium-silicate crystallization phase. The sintering process at 740 °C revealed the formation of a $Na_2Ca_2Si_3O_9$-type crystalline phase (25). The addition of zinc to the Bioglass 45S5 did not significantly influence the structure and composition of crystalline zinc phases (26). X-ray diffraction (XRD) pattern of prepared glass particles yielded Combeite ($Na_2Ca_2Si_3O_9$) as a main crystalline phase (Figure 1).

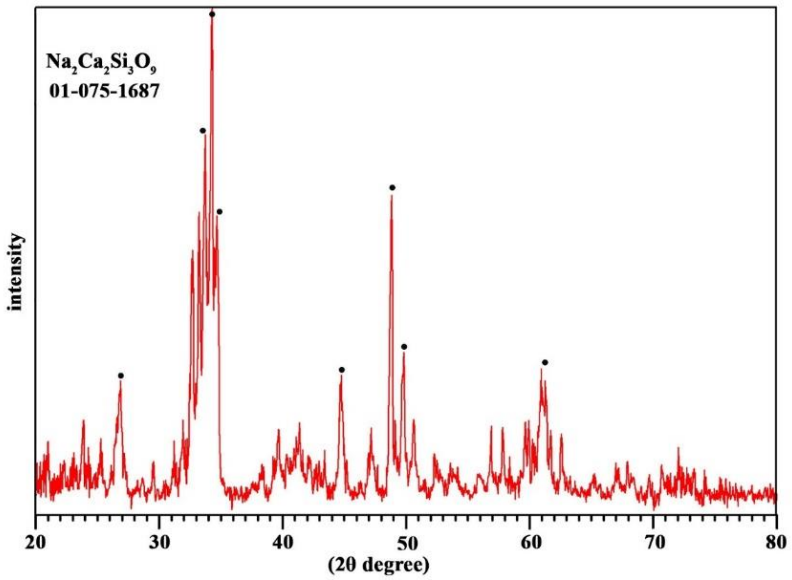


**Figure 1. The XRD spectrum of the synthesized Zn-BAG sample**

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Fourier transform infrared spectroscopy (FTIR) analysis of the synthesized Zn-BAG shows the formation of crystals in the material structure due to sintering at 740 ˚C. Two peaks in the area of 1042 $cm^{-1}$ and 1928 $cm^{-1}$ show the stretching of the Si-O bond in the structure. These two peaks were theoretically developed by splitting the main peak of 1100 $cm^{-1}$ (27). The two peaks in the area of 526 $cm^{-1}$ and 576 $cm^{-1}$ indicate phosphate bond (28). These results were consistent with a crystalline phase in the XRD analysis. Moreover, in both spectra, the presence of some carbonate was detected at the peak of 1384 $cm^{-1}$, which indicates the absorption of $CO_2$ captured from ambient air on the powder structure (Figure 2) (29).

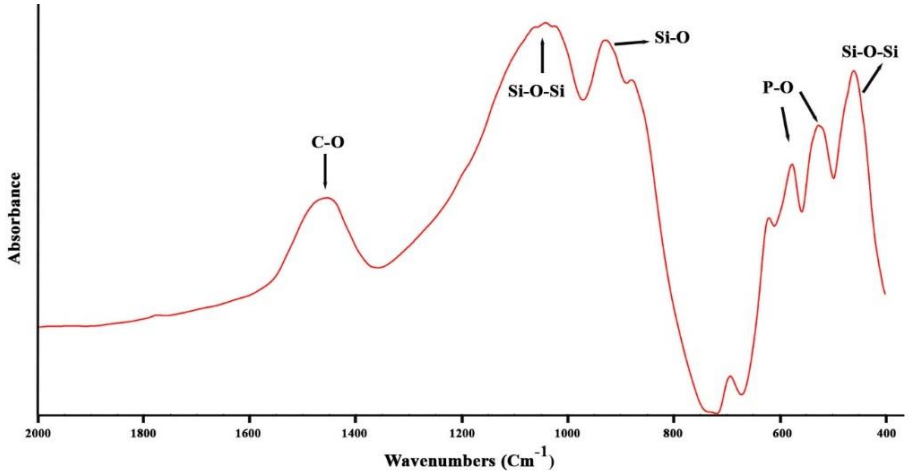


**Figure 2. FT-IR spectrum of Zn-BAG sample**

In scanning electron microscope (SEM) images, Bioglass particles exhibited a plate-like shape with a particle size of less than 100 nm. The EDS analysis confirmed the presence of zinc in the Bioglass structure (Figure 3).

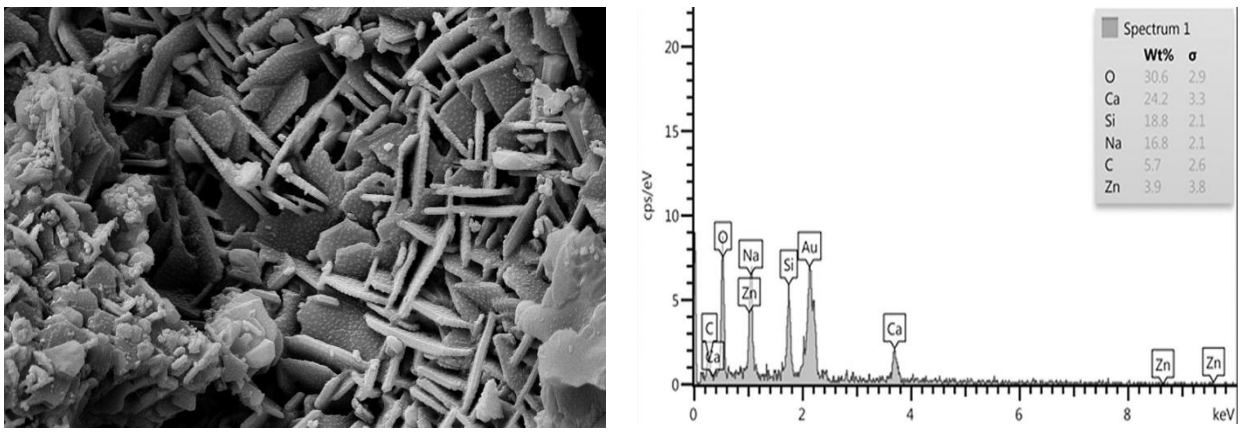


**Figure 3. SEM-EDS analyses**

**Histological analysis:** the pulpal response followed by direct pulp capping with MTA showed no pulpal inflammation in 80% (4 samples) of cases. The pulpal response followed by direct pulp capping with Zn-BAG showed no pulpal inflammation in 60% (3 samples) of cases. There was no significant difference between the type of pulp capping agent and the degree of inflammation.

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In the examination of the location of the dentin bridge formation in the MTA group, in 2 cases (40%) the location of the dentin bridge formation was in the place of exposed pulp, in another 2 cases (40%) in a location other than the exposed pulp, and in the remaining 1 case (20%) it was a combination. In the Zn-BAG group, dentin bridge formation was observed in 3 cases (60%) in the exposed pulp area and in 2 cases (40%) in a place other than the exposed pulp area. However, no significant relationship was observed between the location of the dentin bridge and the type of pulp capping agent. In comparison, the percentage of dental bridge formation in the MTA group was less than 25% in 3 cases (60%), between 25-50% in 1 case (20%) and between 50-75% in 1 case (20%). In the Zn-BAG group, in 4 cases (80%) the percentage of dental bridge formation was less than 25% and in 1 case (20%) it was between 25-50%. There was no significant difference between the type of pulp capping agent and the percentage of dentin bridge formation. The quality of dentine bridge formation in MTA group was found to be without tubules in 1 case (20%), irregular pattern of tubules in 3 cases (60%) and regular pattern of tubules in 1 case (20%). In the Zn-BAG group, the quality of dentine bridge formation was observed in 4 cases (80%) without tubules and in 1 case (20%) irregular pattern of tubules. There was no significant relationship between the type of pulp capping agent and the quality of dentin bridge formation (Figures 4-6).

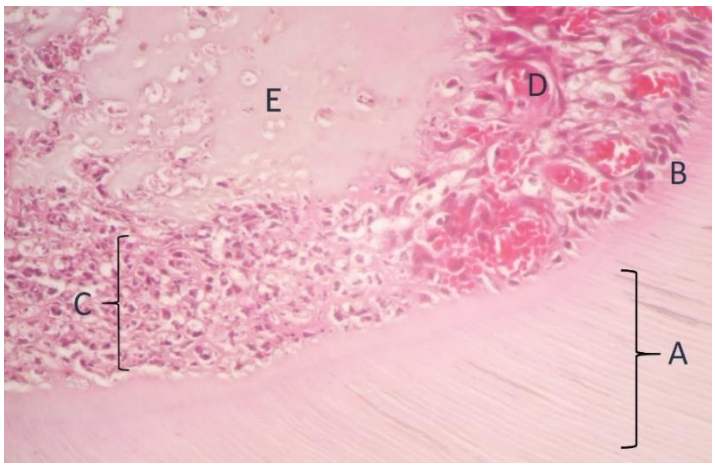


**Figure 4. Hematoxylin-eosin staining evaluation of the effects of the (A) MTA group on direct pulp capping assay. A: Dentin. B: predentin. C: infiltration of inflammatory cells. D: atubular dentin**

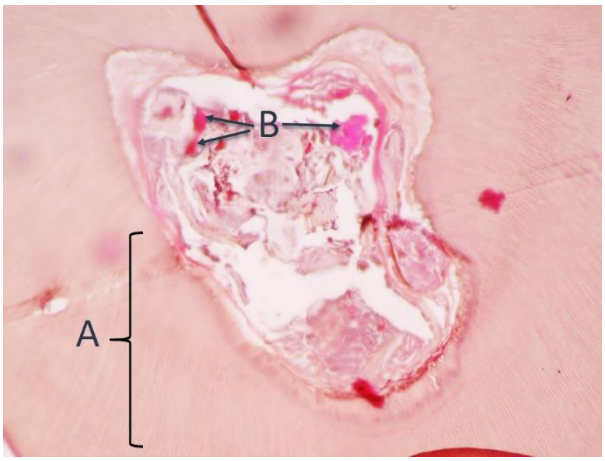


**Figure 5. Hematoxylin-eosin staining evaluation of the effects of the (A) Zn-BAG group on direct pulp capping assay. A: Dentin. B: atubular dentin**

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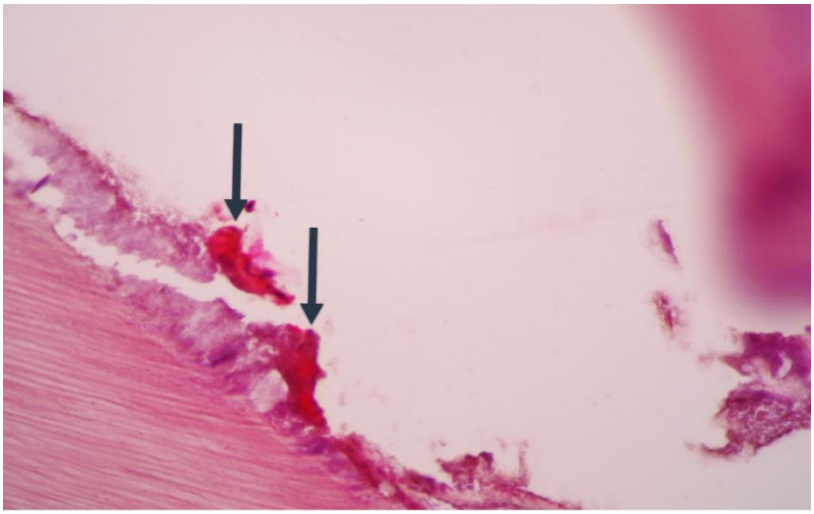

**Figure 6. Formation of autobular dentin at the defect site in the Zn-BAG group**

## Discussion

In this study, Zn-BAG and MTA pulp capping showed similar desirable cellular and inflammatory responses when applied over mechanically exposed rat pulp. Maintaining pulp vitality is decisive for long-term tooth survival. Management of deep caries and exposed pulp can be challenging. Therefore, careful treatment decisions should be made to maintain pulp vitality (30).

Direct pulp capping (DPC) is the preferred treatment option for managing reversible pulpitis (4). Garrocho-Rangel et al., in a systematic review, indicated that DPC agents' clinical and radiographic success rates applied in vital primary teeth with deep carious were satisfactory, and both DPC and pulpotomy can be used as reliable choices for the management of deep carious primary teeth (4). Furthermore, DPC is a conservative treatment and at the same time requires less procedural time than pulpotomy, which is especially important in pediatric dentistry. The success rate of the materials used in DPC depends on the material's properties such as antimicrobial properties, low or no cytotoxicity, maintaining the integrity of pulp tissue, stimulating the reparative dentin formation, and maintaining pulp vitality, and biocompatibility with deciduous pulp tissue (4, 31-33).

The pulpal response to some biomaterials is noticeably different. Various biomaterials have been introduced for vital pulp therapy; however, none of them have been able to meet all the requirements delineated for vital pulp therapy. New alternative materials are developed with high biocompatibility and pulpal response. New pulp capping agents are designed to promote appropriate biological response with biomaterials (34).

MTA has the potential to promote bone and tissue regeneration. Furthermore, MTA has shown good sealing ability and structural stability. When used as a pulp capping material, MTA showed successful outcomes in treating primary teeth (4, 33).

Bioactive glass (BAG) is a new class of biomaterials with antibacterial properties proposed as an adjunct to restorative and esthetic dentistry (6, 10). BAG can promote hard tissue formation and mineralization (6). Recent in vitro studies has shown that bioactive glass and MTA both have the potential to induce dentin bridge formation (15).

Since BAG has a non-crystalline structure, it shows better biological activity than other bioceramics, such as MTA, which have a crystalline structure (14). Davaie et al. suggested the addition of bioactive glass

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to calcium phosphate cement (CPC) enhanced the bioactivity of CPC material (35). Biomaterials with BAG are not yet commercially presented for pulp regeneration (5). Various studies have investigated the effects of BAG on pulp capping (6, 14, 15). Haghgoo et al. concluded that MTA and BAG are both reliable for DPC of primary teeth (6). Long et al. proposed BAG as promising pulp capping material (14). Hanada et al. found that bioactive glass-based material can exhibit satisfactory biocompatibility with the dental pulp and has the potential to be used as a direct pulp capping agent (15).

This study added zinc to bioactive glass as a doping element. When zinc is added to silicate BAGs as a doping element, it postpones the failure of the silicate network by biological fluids. High zinc content delays the development or progress of glass degradation, and only a low visible sign of surface change is evident in such cases (36). Various studies have shown that Zn ions in BAG have beneficial effects on the odontogenic and angiogenic potential of dental pulp stem cells (hDPSCs), which are considered a promising source of cells for functional pulp regeneration and endodontic reconstruction (18, 37). The effect of materials on the formation of odontogenic-like cells by inducing dental pulp cells is a significant element in enhancing the success rate of direct pulp capping (38).

Zhang et al. demonstrated that Zn-BAG combined with calcium phosphate cement had no cytotoxic effects on hDPSCs, which confirms the tissue regeneration potential of the studied materials. The study also found that calcium phosphate cement containing Zn-BAG stimulated alkaline phosphatase (ALP) activity, causing mineral nodules to form and mRNA expression of odontogenic genes such as DSPP, DMP-1, Runx2, and osterix, which indicates the role of Zn-BAG in the odontoblastic differentiation of hDPCs (18).

One of the important functions of zinc in various medical applications of BAGs is its antibacterial activity (36). Paramita et al. showed the enhanced osteogenic effect of zinc-doped Bioglass nanoparticles (Zn-nBGC) compared to nano-Bioglass ceramic nanoparticles (nBGC) (39). Although the antibacterial mechanism of zinc ions in bone metabolism, limited in vitro/in vivo studies are available regarding the biological properties of zinc-containing BAG (36).

Restoration of dental pulp tissue after direct pulp capping with calcium hydroxide in rats is histologically comparable to the healing process described in humans (40). The results of the present study did not show any severe necrosis and inflammation in any of the samples of the MTA or Zn-BAG groups, which may be attributed to the antibacterial properties and biocompatibility of these two materials. In a study by Haghgoo et al., no necrosis or severe inflammation was observed in any of the investigated samples following the use of MTA and BAG (6).

This study showed that the percentage of dentin bridge formation between BAG and MTA is not statistically significant. Zn-BAG induced reparative dentin formation at the site of pulp exposure. The highest percentage of dentin bridge formation was found in the MTA group, but there was no significant difference in dentin bridge formation between MTA and Zn-BAG. One of the essential properties of the material suitable for pulp capping is the property of not causing pulpal inflammation; less inflammation of the pulp may indicate better biocompatibility of pulp capping materials (41). Thus, lower level of inflammation is a key factor for the success of pulp-capping materials; however, dentin bridge formation alone is not a valuable factor for establishing the pulpal health status. In the present study, no significant difference was found between MTA and Zn-BAG and the quality of dentin bridge formation. Atubular dentin has been found to act as a barrier to bonding agents and toxic substance penetration. Few studies have suggested that the primarily formed atubular dentin or osteodentin can increasingly line with odontoblast-like cells and form tubular dentin during a particular period (42, 43).

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It is suggested to use carrier-mediated use of Zn-BAG in future studies and investigate its effect separately.

When applied over mechanically exposed rat pulp, zn-BAG and MTA pulp capping showed similar desirable cellular and inflammatory responses in this study. Zn-BAG is a promising candidate for pulp capping material. Further studies are needed to investigate the mechanical properties of BAG.

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