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Comparison of cell viability and cytotoxicity of MTA, 45S5 and niobiophosphate bioactive glass

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Aim: This current in vitro study investigated the cytotoxicity and the ability to maintain cell viability of two bioglasses, the commercial 45S5 (Sylc®, OSspray Ltd, London, UK) and the experimental NbG (niobiophosphate bioactive glass), in comparison to MTA (MTA Angelus®, Parana, Brazil). **Methods:** In the cell viability assay, human gingival fibroblasts were exposed to the bioactive materials/cements (NbG; 45S5; and MTA) diluted in the cell culture medium. According to ISO 10993-5, a cytotoxic effect was considered when there was a decrease in cell viability of more than 30%. The three bioactive materials were also analyzed under SEM (TM 3030, Hitachi, Tokyo, Japan) to assess the mean particle size, and under EDX analysis (EDX-720, Shimadzu, Tokyo, Japan) to verify composition and the presence of contaminants. **Results:** Human gingival fibroblasts had the highest cell viability when exposed to NbG ($p<0.001$). The control group and the MTA group had similar values ($p=0.2341$). The lowest cell viability occurred for the 45S5 group ($p<0.001$). The average particle size of the materials tested was 5.2µm for 45S5; 54.0µm for NbG; and 4.0µm for MTA. 45S5 and NbG showed the presence of Si, Ca, and P. **Conclusion:** The 45S5 bioglass was cytotoxic to fibroblasts, while MTA was not. The addition of niobium into the bioglass composition is advantageous.

Keywords: Materials testing. Bioglass 45S5. Root canal filling materials. Fibroblasts. Silicates.

Introduction

More than 70% of cases of deep dental caries may lead to the exposure of viable pulp tissue. Therefore, vital pulp therapies (such as direct pulp capping and pulpotomy) are the treatments of choice when the pulp tissue condition is favorable[1]. The selection of the material/cement to use over the vital tissue may directly influence the treatment's success, because the pulp tissue requires a biocompatible material, with antibacterial potential and capable of inducing cell differentiation, which will consequently influence the formation of repairing dentin[2].

The original mineral trioxide aggregate (MTA) and several other related materials are the current materials of choice for vital pulp therapy. MTA is a biocompatible calcium silicate-based cement and is regarded as the gold standard primarily because it promotes the migration of stem cells from the dental pulp, inducing the formation of mineralized tissue to repair the pulp-dentin interface without causing significant inflammation[3-6]. Although MTA has numerous adequate properties, it also has some drawbacks, such as difficulties in handling and cases of staining the tooth structure[7]. These drawbacks were some of the triggers for researchers to study and launch other products.

One of the materials that has been investigated and proposed as a potential option for vital pulp therapy is 45S5 bioactive glass. Introduced in dentistry in 1969 by Professor Larry Hench, this bioglass was recognized as an osteoinductive substance. Today, bioactive glass is incorporated into desensitizing agents, adhesive materials, varnishes, and toothpastes[8]. This biomaterial has a noncrystalline structure and has shown better bioactivity than other bioceramic materials that have a crystalline structure, such as MTA and iRoot BP Plus[9]. The 45S5 bioglass also has good antibacterial activity[8] and the ability to induce proliferation, differentiation, and mineralization of human dental pulp cells[2,10]. However, some disadvantages of 45S5 include chemical instability and high solubility[11]. In dental research, other bioactive glasses, such as the niobium phosphate-based, have been developed. The niobium phosphate bioglass (NbG) also releases ions, which are able to induce the formation of mineralized precipitates[12,13], and, at the same time, present higher chemical stability compared to 45S5. This stability is a consequence of the chemical bonding that is formed on the glass surface, and it is composed of layers of niobium dioxide (Nb-O-Nb-O)[14-17].

This study aimed to evaluate the cytotoxicity in fibroblasts of two bioactive glasses: 45S5 (Sylc®, OSspray Ltd, London, UK) and an experimental niobium phosphate (NbG) (niobium phosphate bioactive glass); compared to MTA (MTA Angelus®, Paraná, Brazil). Cytotoxicity is a critical factor in the development of dental materials, particularly those intended to promote cell proliferation. Therefore, the results obtained in this study may guide the development of new materials designed to protect and repair the vitality of pulp tissue.

Materials and Methods

This in vitro study tested the cytotoxicity of three materials/cements on human gingival fibroblasts: 1) an experimental niobium phosphate bioactive glass (NbG) that was

formulated as shown in the text below; 2) a commercial bioactive glass with calcium sodium phosphosilicate (45S5, Sylc®, OSspray Ltd, London, UK); and 3) a gold standard calcium silicate-based cement (MTA, MTA Angelus®, Paraná, Brazil). A control group considered fibroblasts without treatment.

Production of the NbG

The preparation of NbG consisted of melting mixtures of diammonium phosphate (Reagent Grade - Casa Americana, São Paulo, SP, Brazil), niobium oxide (Optical Grade - Companhia Brasileira de Mineração e Metalurgia, Araxá, MG, Brazil), calcium oxide (Reagent Grade – Casa Americana), and sodium carbonate (Reagent Grade - Casa Americana). The chemical compounds were mixed in a shaker mixer for 1 hour, placed in an alumina crucible, and heated in an electric furnace (Lindberg, Blue M, IL, USA). The heating rate was 10ºC/min up to 500°C, and the material was kept in the air at this temperature for 30 minutes to eliminate volatile products. The material was then heated to 1400°C to completely melt the precursors, maintaining this temperature for 20 minutes, which allowed it to homogenize and eliminate bubbles. The liquid was poured into a stainless-steel mold and cooled at room temperature. The glass was then crushed in a vibrating system with a tungsten ball (Pulverisette, Fristsch, Idar-Oberstein, RP, Germany) for 30 minutes. The resultant powder was passed through a series of sieves of 150µm, 75µm, and 53µm (Hogentogler & Co., Inc., Columbia, MD, USA). The particle size distribution was determined by laser diffraction using a particle size analyzer (CILAS Model 1064, Compagnie Industrielle des Lasers, Orléans, France). Additional information about the development and composition of NbG may be found in our previous publications[11,15,16].

Cell culture - human gingival fibroblasts

Human gingival fibroblasts (HGF, American Type Culture Collection - ATCC® CRL-2014TM) were maintained in Dulbecco's Modified Eagle Medium (DMEM; Gibco®) enriched with 10% fetal bovine serum (FBS; Atlanta Biologicals®), 100 U/mL penicillin, 100 µg/mL streptomycin, and cultured in a humidified atmosphere of 5% CO2 in air.

Cell viability assay

Fibroblasts seeded in 96-well plates (6x10⁴ cells/mL) were exposed to different bioactive materials/cements (NbG; 45S5; and MTA) diluted in the cell culture medium. Briefly, a solution containing 5 mg/mL of each material was prepared, and then 200 µL (corresponding to 1 mg of the bioactive compound) was added into the wells. After 24 hours, the medium was replaced with a new one containing DMEM and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, 0.5%). Plates were incubated for 3 hours (37°C, humid atmosphere, 5% CO2) and protected from light. Then, the medium was changed to 1% sodium dodecyl sulfate (SDS) (100 µL/well), and spectrophotometric readings were performed at 550 nm. All experimental groups were conducted in triplicate, with the appropriate controls. Cell viability was considered as: % Viability = TA / T1 x 100, where TA: cell viability obtained from treated cells; T1: cell viability obtained from untreated (control) cells. According to ISO 10993-5, a cytotoxic effect was considered with a decrease in cell viability of more than 30%.

Characterization of bioactive materials/cements: Scanning Electron Microscopy (SEM) and Energy-Dispersive X-ray Fluorescence Spectrometry (EDX)

The three bioactive materials were analyzed under SEM (TM 3030, Hitachi, Tokyo, Japan) to measure and assess the mean particle size. Images were taken at 500x and 2000x magnifications with 15kV acceleration. An EDX analysis (EDX-720, Shimadzu, Tokyo, Japan) was performed to verify the final composition and the presence of possible contaminants in the bioactive material. A CCD (charge-coupled device) camera was used to select an area of 10 mm in diameter. This procedure is considered appropriate to determine the composition of the whole material[18]

Data Analysis

Statistical analysis was performed using SigmaPlot 13 software (SigmaPlot v. 13.0, Systat Software Inc., San Jose, USA). The normality and equality of variance assumptions were statistically analyzed by the Shapiro-Wilk test and Brown-Forsythe test (α = 5%). Cell viability data were submitted to One-Way and Holm-Sidak ANOVA for the contrast between means (α = 5%). Data resulting from SEM and EDX were descriptively reported.

Results

The highest cell viability values were statistically significant for the NbG group samples (p<0.001). The control group and the MTA group had similar values (p=0.2341). The lowest cell viability value occurred in the 45S5 group (p<0.001). The mean and standard deviation of cell viability (of human gingival fibroblasts) after treatment with the tested cements/materials are presented in Figure 1.

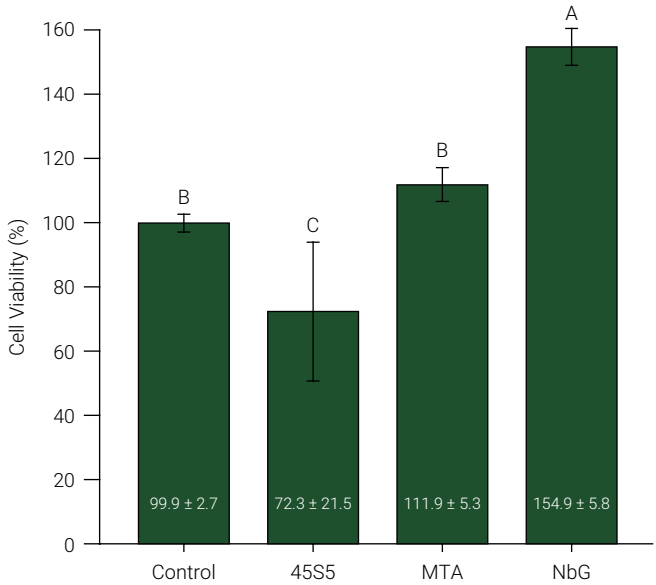

Figure 1. Mean and standard deviation of cell viability (of human gingival fibroblasts) after treatment with the tested cements/materials: NbG (experimental niobiophosphate bioactive glass); 45S5 (commercial bioactive glass with calcium sodium phosphosilicate); and MTA (MTA Angelus®, a commercial calcium silicate-based cement).

SEM showed that the average particle size of the materials tested was 5.2µm for 45S5; 54.0µm for NbG; and 4.0µm for MTA. Figure 2 shows a representative image from one sample pertaining to each one of the materials/groups.

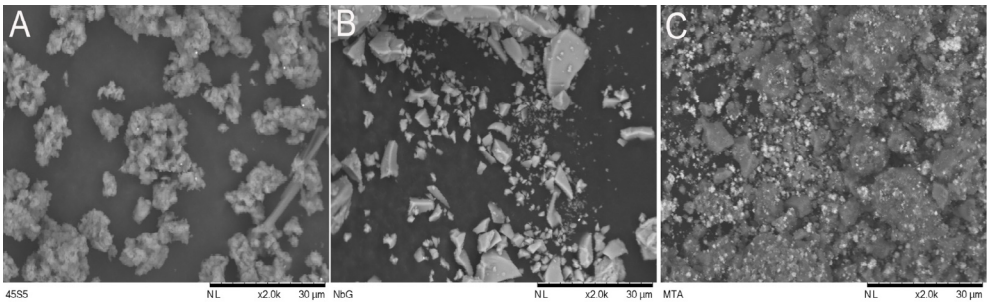

Figure 2. SEM images showing the average particle size of the materials tested. The average particle sizes of NbG (experimental niobiophosphate bioactive glass) (image B), 45S5 (commercial bioactive glass with calcium sodium phosphosilicate) (image A), and MTA (MTA Angelus®) (image C) were 54.0µm, 5.2µm, and 4.0µm, respectively.

Table 1. Chemical composition of 45S5 and NbG experimental glass detected by the Energy-Dispersive X-ray fluorescence spectrometry (EDX); and particle size assessed with Scanning Electron Microscopy (SEM).

Bioactive Glass/ cement	Particle size average (µm)	Composition
45S5	(5.2 µm)	SiO2 36,8%, Na2O 42,8% CaO 13.9%, P2O5 6.5%
NbG	(54.0 µm)	Nb2O5 41.8%, P2O5 32.5%, CaO 18.8%, Al2O3 2.7%, Na2O 1.2%, SrO 0.04%

Discussion

This study used a cell viability assay, an image assessment, and a chemical composition test to investigate materials that are promising for several areas of application in dentistry, such as vital pulp therapies. Bioactive glasses (experimental NbG and 45S5) were compared to MTA, a gold standard cement in endodontics.

Our main results showed that 45S5 bioactive glass had a cytotoxic effect, as it induced the lowest cell viability, while NbG promoted the highest cell viability. MTA showed good cell viability results, similar to the control group.

The effect of MTA on cell viability can be related to the presence of silicates in the MTA composition[19,20]. The literature is consistent in showing that MTA induces mineralization and has no detrimental effect on cells[19,21]. When MTA (MTA Angelus®) was tested on human dental pulp stem cells, there was a significant increase in terms of viability, with results superior to those of the control group; a cell migration rate within the normal range; and a high rate of cell proliferation[22]. A recent meta-analysis of several in vivo and in vitro studies found that capping agents exhibited favorable

bioactivity in human dental pulp cells, concluding that calcium silicate-based cements enhanced bioactivity while maintaining adequate cell viability[20].

The present results support other appropriate findings that our research group has been acquiring in relation to NbG. The addition of niobium to the bioglass composition is advantageous because it creates a material with greater chemical durability and biocompatibility[23,24]. This current in vitro experiment showed that NbG increased cell viability (and this effect was higher than that in the control group and higher than that in the MTA group). Likewise, a previous study evaluated the cytotoxicity of bioceramic cements incorporated with 45S5 or NbG bioactive glass particles and found a greater difference in cell viability favoring the cements incorporated with bioglasses compared to conventional bioceramic cements MTA Fillapex and BC Sealer[11]. NbG releases ions, which are capable of inducing the formation of mineralized precipitates and have greater chemical stability[13]. It seems to be a promising material, with a higher level of biocompatibility and a lower level of aqueous dissolution[25]. This may justify the result of the present study, where NbG showed greater cell viability and lower cytotoxicity. Obata et al.[25] (2012) observed that the effects of niobium ions also seem to affect the induction of differentiation and mineralization of osteogenic cells, adhesion, or initial proliferation, which depends on the concentration of ions. Another important aspect is that the presence of niobium in bioactive glass in the development of dental materials could also stabilize the pH[16,23-26].

The cytotoxic effect observed with 45S5 bioglass in the present study is different from some previous articles. In 2015, authors assessed the bioactivity of calcium phosphate-based cements incorporated with bioglass nanoparticles in human dental pulp cells and found increased mineralizing activity, as well as in the tubular structure of endothelial cells, without any cytotoxic effect[19]. This present study may show three reasons for the cytotoxic effect of 45S5 bioglass: the particle size, the high number of ions, and the variation in pH of the medium.

The SEM images showed a clear difference in the size of the particles between the two bioglass materials, with 45S5 being much smaller compared to NbG. This may support the idea that there is a relationship between size and the generation of an inflammatory response. Previous in vitro experiments have shown that micro-sized particles were more susceptible to phagocytosis by macrophages compared to macroparticles; however, microparticles had the power to generate a more intense inflammatory response[27]. Other authors also found that 45S5 with a relatively small particle size (134 times larger than ours) had poor adaptation to the dentin substrate and caused pulp inflammation[28]. In 2021, Ramenzoni et al.[28] used bioglass with a size similar to the present study to investigate inflammatory reactions and osteolysis associated with peri-implantitis and observed that the cytotoxicity of the glass group was higher compared to the control group, especially when there were higher concentrations of glass, regardless of exposure time. Our results, combined with the above-mentioned studies, raise a question about the association of particle size and the concentration of bioactive glass 45S5 as factors that could lead to the generation of inflammation.

Different types and concentrations of ions may be found in the adjacent dentin of teeth treated with direct pulp capping with bioglasses, such as Mg, Si, Na, Al, and Fe. The presence of these ions indicates the existence of ionic exchange between the substrate and the material[29]. The Zn-ion in 45S5 bioglass might be toxic for certain types of human osteoblasts when placed in a concentration greater than ≥ 5%—the cytotoxicity is a result of the concentration of Zn^{2+} ions that are released during bioglass dissolution[3]. A high concentration of calcium ions (88–109 ppm) is considered toxic to human osteoblasts and reduces the ability of osteoblasts to proliferate[30-32].

Another factor that may also be related to the lower rate of cell viability caused by the 45S5 bioactive glass is the variation in the pH of the medium. When the bioactive glass encounters water-based solutions, an ionic exchange occurs at the material/solution interface, leading to a rapid increase in the pH of the solution due to the replacement of H^+ ions by metallic cations. This factor influences the mechanisms of cellular respiration and causes alterations and enzymatic modifications in the diffusion of nutrients and gases to the cells[32].

The primary objective of direct pulp capping is to preserve the integrity of the pulp tissue under various pathological conditions of exposure. Maintaining pulp vitality is essential to prevent additional complications that may necessitate endodontic therapy, particularly in young permanent teeth, thereby allowing for greater preservation of tooth structure[33]. The ideal material should not induce pulpal inflammation, which can lead to necrosis, and it should promote the regeneration of high-quality dentin around exposure. It is important to note that these materials are typically used in situations where the underlying tissue may be inflamed; however, in the present study, fibroblasts were utilized under normal conditions.

A limitation of this study is that it was conducted in vitro, meaning it does not fully replicate the complex conditions present in a living organism. As a result, the findings may not necessarily reflect how these materials behave in vivo, since the human body's environment can influence the materials' cytotoxicity and cell viability in different ways. Additionally, the study exclusively used human gingival fibroblasts, which may not represent the full range of biological responses from other cell types or tissues that these materials could interact with in clinical applications.

In conclusion, the 45S5 bioglass was cytotoxic to fibroblasts, whilst MTA had no cytotoxic effect, and NbG increased cell viability.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no conflict of interest.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Author Contribution

Bruna Laís Lins Gonçalves: Methodology, Investigation, Writing—original draft preparation. **Amanda Palmeira de Arruda Nogueira**: Methodology, Investigation, Writing—review and editing. **Maria Eduarda Fernandes Brito**: Investigation. **Patrícia Maria Wiziack Zago**: Conceptualization, Data curation. **José Bauer**: Conceptualization, Validation, Resources. **Cyrene Piazera Silva Costa**: Methodology. **Meire Coelho Ferreira**: Validation. **Renata Grazziotin-Soares**: Writing—review and editing. **Ceci Nunes Carvalho**: Conceptualization, Formal analysis, Resources, Writing—original draft preparation, Writing—review and editing, Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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