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Biocompatibility and bioactive potential of new bioceramic sealers in rat bone tissue: histological analysis

Biocompatibilidade e potencial bioativo de novos selantes biocerâmicos em tecido ósseo de rato: análise histológica

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ABSTRACT

Objective: Sealer Plus BC and Bio-C Sealer are new silicate-based sealers. We aimed to evaluate the biocompatibility and bioactivity of these silicate-based endodontic sealers compared to that of AH Plus epoxy resin sealer. **Material and Methods:** Fifteen rats underwent a surgical procedure to create a cavity in the tibial bone, where the sealer was inserted according to the group. The animals were euthanized after postoperative period of 15 days. Histological analysis was made, and the results were scored according to the signs of repair, quality of the bone tissue, and presence of inflammation. ANOVA Kruskal-Wallis and Mann-Whitney tests ($p < 0.05$) were performed. **Results:** Sealer Plus BC showed neoformation or presence of bone tissue in 73.33% of samples. Bio-C Sealer showed connective tissue in differentiation or presence of bone in 66.66%. AH Plus showed 80% ($p = 0.01$) of the samples with granulated tissue in the bone defect. Sealer Plus BC presented 46.66% of samples with absence of inflammatory cells and Bio-C Sealer showed moderate inflammatory process in 66.66% ($p = 0.02$). **Conclusion:** The two silicate-based sealers presented better biocompatibility and bioactivity compared to AH Plus epoxy resin sealer.

KEYWORDS

Animal Model; Calcium Silicate; Endontics; Endodontic obturation; Material testing.

RESUMO

Objetivo: Sealer Plus BC e Bio-C Sealer são novos selantes à base de silicato. Nosso objetivo foi avaliar a biocompatibilidade e bioatividade desses cimentos endodônticos à base de silicato em comparação com o cimento de resina epóxi AH Plus. **Material e Métodos:** Quinze ratos foram submetidos a procedimento cirúrgico para confecção de cavidade no osso tibial, onde foi inserido o cimento de acordo com o grupo. Os animais foram eutanasiados após 15 dias de pós-operatório. Foi feita análise histológica e os resultados foram pontuados de acordo com sinais de reparo, qualidade do tecido ósseo e presença de inflamação. Foram realizados testes ANOVA Kruskal-Wallis e Mann-Whitney ($p<0,05$). **Resultados:** O Sealer Plus BC apresentou neoformação ou presença de tecido ósseo em 73,33% das amostras. O Bio-C Sealer apresentou tecido conjuntivo em diferenciação ou presença de osso em 66,66%. O AH Plus apresentou 80% ($p = 0,01$) das amostras com tecido granulado no defeito ósseo. O Sealer Plus BC apresentou 46,66% de amostras com ausência de células inflamatórias e o Bio-C Sealer apresentou processo inflamatório moderado em 66,66% ($p = 0,02$). **Conclusão:** Os dois cimentos à base de silicatos apresentaram melhor biocompatibilidade e bioatividade em relação ao cimento resina epóxi AH Plus.

PALAVRAS-CHAVE

Modelo Animal; Silicato de cálcio; Endodontia; Obturação endodôntica; Teste de materiais.

INTRODUCTION

To understand the material–tissue interaction is critical to improving the biomaterial-assisted healing process; therefore; studies have focused on assessing biocompatibility [1], considering that root canal sealers can be extruded into the periapical medullary bone producing harmful effects like additional inflammation, and foreign body reactions [2]. Bone tissue has a complex structure, and researchers have sought to study materials capable of repairing structural defects. In recent years, attention has been paid to the potential of bioactive materials, including bioceramics, given the possibility of favorable interaction for tissue repair [3].

Bioceramic sealers have advantages as biocompatibility, presence of calcium phosphate in their composition, they are non-toxic and non-absorbable, generally recognized as inducers of bone formation [4-6]. It has been reported the importance of hydraulic calcium silicate cements as advantageous root sealers like filling bone defects [2,4]. Given their physicochemical and biological characteristics, calcium silicate sealers have obtained similar or superior results to conventional cements both in vitro and in vivo [7]. Animal models are indispensable for testing bone-substitute biomaterials. The small animal models, including rats, are beneficial because they have easy handling and a life span suitable for observation [8-12].

Sealer Plus BC is a calcium silicate-based material with excellent biochemical properties known to promote an increase in pH [6], which is thought to be associated with calcium release and thus accelerated healing [13,14]. Bio-C Sealer is another premixed sealer containing calcium silicates in this composition [15]. This material can induce mineralization according to the release of calcium ions [16] and present alkalinity ability [17].

This primary goal of this work was to compare the biocompatibility and bioactivity of these two silicate-based endodontic sealers with that of AH Plus resin cement, which has a long history of use due to its faster setting time, lower solubility, lower film thickness and higher radiopacity compared to other materials . We focused on the mineralized-tissue-inducing capacity according to tissue scores of formation and quality, maturation score, and degree of inflammation. The null hypothesis is that have no difference between the bone healing provide by bioceramics or epoxy resin sealers.

MATERIAL AND METHODS

Animals

The research protocol was approved by the Animal Use Ethics Committee of Piaui State University (protocol no.: 0175/2018). We used 15 male rats (Rattus norvegicus albinus, Wistar; 250–300 g; 8–12-weeks old). The animals were kept in clean cages (n = 5/cage) with litter bedding and a 12-hour light/dark cycle. Animals were provided a normal diet and water ad libitum.

The animals were used to assess biocompatibility and bioactivity according to the bone regeneration-inducing capacities of Sealer Plus BC (lot no.: WR770100; MK Life, Porto Alegre, Rio Grande do Sul, Brazil; composition: zirconium oxide, tricalcium silicate, dicalcium silicate, calcium hydroxide, and propylene glycol) and Bio-C Sealer (lot no.: 45225; Angelus, Londrina, Paraná, Brazil; composition: calcium silicates, calcium aluminate, calcium oxide, zirconium oxide, iron oxide, silicon dioxide, and dispersing agent) relative to AH Plus (lot no.: 337957J; Dentsply DeTrey, Konstanz, Baden-Württemberg, Germany).

To understand the bone-healing process associated with these materials, we created a bone defect. For this purpose, animals were randomly assigned to three groups: group 1, Sealer Plus BC cement test; group 2, Bio-C Sealer; and group 3, AH Plus. We used five animals per group based on previous studies [18-20].

Surgical procedure

At 1 h before the procedure, dipyrone was applied subcutaneously (160 mg/kg). The rats were weighed and then intraperitoneally injected with 100 mg/kg of ketamine combined with 10 mg/kg of xylazine for general anesthesia. Trichotomy was performed in the right hind leg, followed by disinfection with polyvinylpyrridoline-iodine and incision with a No. 15 scalpel blade. When visualizing the tibial bone tissue, a cavity was prepared using a low-speed dental drill (Kerr, Sollentuna, Sweden) with isotonic saline irrigation. The size of the defect was 2.3 mm in diameter. The cements were prepared according to manufacturer guidelines and applied immediately after handling, filling the entire cavity. Subsequently, the wound was sutured with 3-0 nylon thread and washed with polyvinylpyrrolidone-iodine.

Tetracycline antibiotic was administered in a single dose (20 mg/kg) immediately after surgery. At 12-h post-surgery, subcutaneous dipyrone (160 mg/kg) was used. Given that this was a preliminary study, we adopted a short timeline for evaluation (i.e., a single time point was chosen according to previous studies to analyze initial healing progressing) [14,15]. At 15-days post-surgery, the animals were euthanized by tiopental overdose (100 mg/kg) according to the recommendations of the Panel on Euthanasia of the American Association of Veterinary Medicine, and tibial samples were collected for histologic analysis.

Histology

The right tibia was harvested and immediately fixed in 10% formaldehyde in buffer. After 24 h, the tissue was immersed in decalcifying solution (4% nitric acid) until softened, followed by washing and paraffinization. Each sample was sliced into three pieces, resulting in 15 per group. Hematoxylin and eosin staining was performed for histologic analysis to evaluate the formation and quality of bone tissue, degree of collagen maturation, tissue mineral density, and degree of inflammation. The definition of the histological scores (Table I) was based on previously established standardized scores [14] adapted from literature [21-24]. The analysis was performed by a blind professional.

Statistical analysis

SPSS statistical software (v.21.0; IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. Nonparametric comparative analyses were performed between groups. According to the sample characteristics and the 15 units per group, a one-factor Kruskal–Wallis analysis of variance test was performed in three groups for each of the three parameters analyzed, which allowed verification of the average of the ranks for each of the groups. The results were supported by Mann–Whitney U tests for comparison of two groups. The level of significance considered was $p < 0.05$.

RESULTS

In the formation and quality of the newly formed tissue (Tables II(A) and III(A)) Sealer Plus BC show bone neoformation or presence of bone

Table I. Histological scores

Score (A)	Bone tissue formation and quality score
1	Tissue neoformation (defect filled with connective tissue containing blood capillaries, fibroblasts, macrophages, and collagen fiber neoformation)
2	Dense connective tissue suggesting differentiation into bone tissue with the presence of many cells and fibers in the process of organization
3	Bone neoformation, in which connective tissue is in the process of differentiation, forming bone matrix, or osteon
4	Presence of bone tissue
Score (B)	**Degree of collagen maturation and tissue mineral density scores**
1	No sign of bone union, bed filling with connective tissue
2	Osteon (formation of connective tissue in bone with osteoprogenitor and osteogenic cells)
3	Isolated spicules of immature bone
4	Compact bone formation
Score (C)	**Degree of inflammation score**
1	Absence of inflammatory cells
2	Moderate presence of inflammatory cells
3	Intense presence of inflammatory cells

Table II. Distribution of groups according to sum and average of posts

(A) Bone quality scores	
Group	**Average of posts**
1 - Sealer Plus BC	28.00
2 - Bio-C Sealer	27.10
3 - AH Plus	13.90

Note: $\chi^2 = 12,06$; gl = 2; p = 0,01.

(B) Tissue maturation scores	
Group	**Average of posts**
1 - Sealer Plus BC	27.77
2 - Bio-C Sealer	27.10
3 - AH Plus	14.13

Note: $\chi^2 = 11,07$; gl = 2; p = 0,01

(C) Inflammation degree scores	
Group	**Average of posts**
1 - Sealer Plus BC	16.67
2 - Bio-C Sealer	29.03
3 - AH Plus	23.30

Note: $\chi^2 = 7,37$; gl = 2; p = 0,02.

Table III. Comparisons between groups

(A) Bone quality scores		
Compared samples	**Difference between averages**	**Statistical significance**
Group 1 × Group 2	0.46	0.87
Group 1 × Group 3	10.46	0.01*
Group 2 × Group 3	7.74	0.01*
(B) Tissue maturation scores		
Compared samples	**Difference between averages**	**Statistical significance**
Group 1 × Group 2	0.34	0.94
Group 1 × Group 3	8.90	0.01*
Group 2 × Group 3	7.96	0.01*
(C) Inflammation degree scores		
Compared samples	**Difference between averages**	**Statistical significance**
Group 1 × Group 2	7.74	0.02*
Group 1 × Group 3	4.94	0.09
Group 2 × Group 3	4.34	0.15

Note: *p < 0,05 (significant).

tissue in 73.33% of samples, dense connective tissue in 20% and defect filled with connective tissue in 6.66%. Bio-C Sealer have 66.66% in which connective tissue is in the process of differentiation or presence of bone tissue and 33.33% presented tissue neoformation. These two groups differed (p = 0.01) from AH Plus (Table II(A) and III(A)) which have 80% of the samples in the initial tissue-repair phase with a predominance of granulated tissue in the bone defect (Figure 1e and f), 13.33% have bone neoformation and 6.66% presented bone tissue.

Degree of collagen maturation parameter (Tables II(B) and III(B)) in Sealer Plus BC presented 66.66% of samples with isolated spicules of immature bone, in 26.66% have connective tissue and no bone union in 6.66%. Bio-C Sealer have isolated spicules in 53.33% of samples, show compact bone in 13.33% (Figure 1b and d), osteon was present in 6.66% and 26.66% bed filling with connective tissue. AH Plus differed (p = 0.01) from the other groups, with no sign of bone union in 73.33%, isolated spicules in 20% and connective tissue with osteoprogenitor and osteogenic cells in 6.66%.

According to the inflammation parameter (Tables II(C) and III(C)), the Sealer Plus BC displayed 46.66% of slides with an absence of inflammatory cells, 46.66% of moderate inflammation and 6.66% with intense presence of inflammatory cells. Bio-C Sealer show 66.66% with moderate inflammatory process, in 20% intense presence of inflammatory cells and 13.33% with absent of inflammatory. AH Plus showed 26.66% of samples with an absence of inflammatory cells, 40% with moderate inflammatory infiltrate and 33.33% with intense inflammation. The difference (p = 0.02) in this parameter was between Sealer Plus BC and Bio-C Sealer.

DISCUSSION

According to the degree of collagen maturation, the bioceramic cements presented no difference results between them, with presence of bone tissue or connective tissue differentiation forming bone matrix in most samples and allowing good maturation of the bone tissue along with the presence of compact bone in some laminae. This was similar to a study in which all bioceramic sealers promoted repair in mineral tissue and supports the concept that if a material provides tissue deposition, it also promotes the healing process [25,26]. The results associated with AH Plus were different from those of the bioceramic cements, with majority of the tissue samples showing initial tissue formation and presenting the bone defect filled only by connective tissue.

Tissue neoformation might be associated with properties of calcium ion release, which provides mineral deposition [27]. Si-containing ionic products are as important as calcium because their release can promote osteogenic differentiation of stem cells [28]. The amount of calcium released by bioceramic cements is superior to that by AH Plus [29], which is in line with the higher mineralization observed by Sealer Plus BC and Bio-C Sealer in the present study. A previous study reported that the presence of AH Plus does not significantly interfere with the repair process, because neoformation of bone tissue in contact with this cement progressed like that of an empty control cavity [30]. Another study suggested that AH Plus does not induce calcium release or alkalizing activity [31]. Collectively, these results suggest that the biocompatibility of AH Plus is due to its lack of interference in the physiological repair process.

The availability of calcium ions is associated with a process that favors an alkaline pH essential for the establishment of a formative matrix, which in turn accelerates the tissue-healing

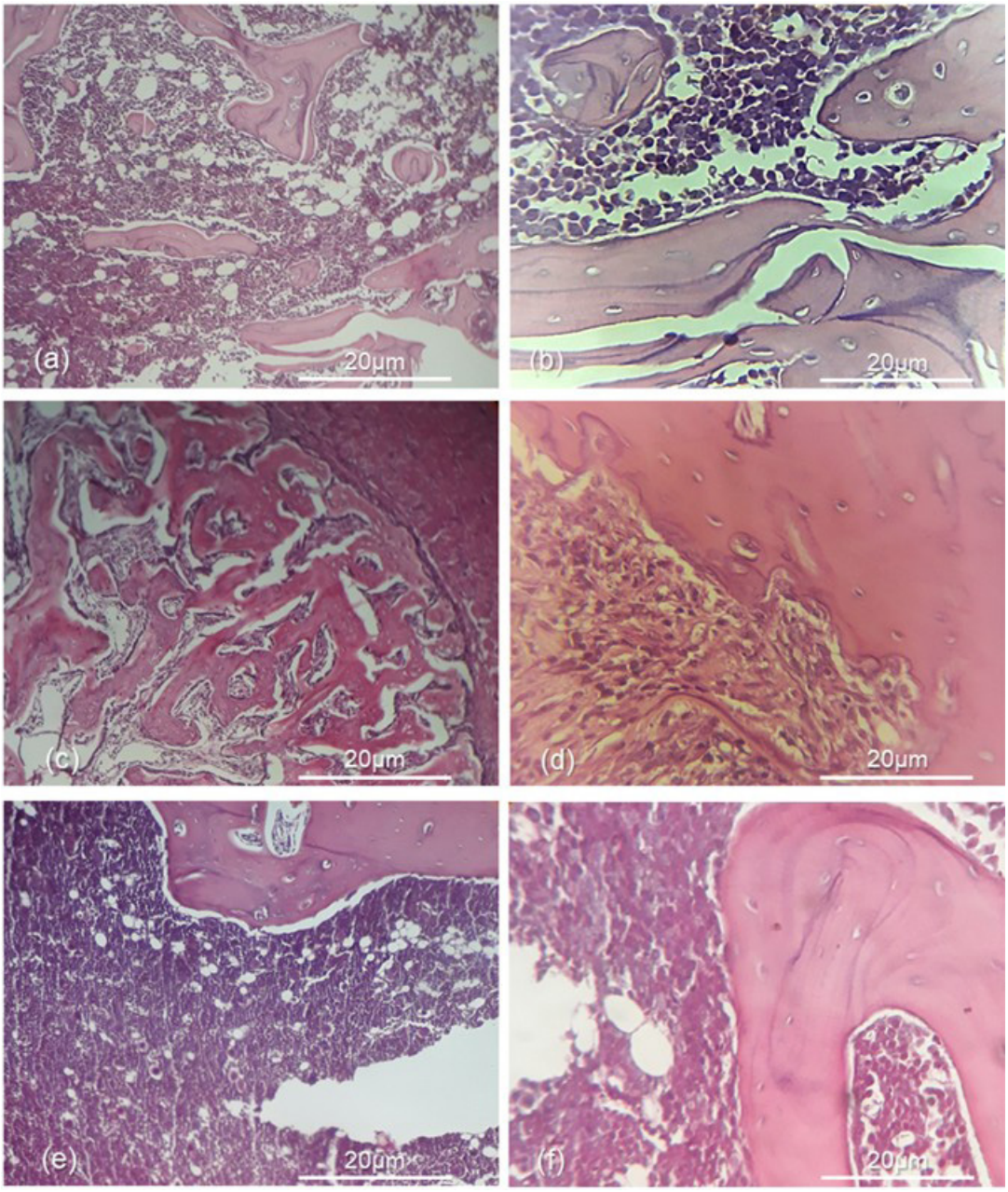

Figure 1 - H&E histological images demonstrating the bone tissue response after contact with obturator materials. Sealer Plus BC group 10 (a) and 40 (b) magnification showing bone neoformation with bone matrix suggesting differentiation for bone tissue, and presence of osteoprogenitor and osteogenic cells. Bio-C Sealer Group 10 (c) and 40 (d) magnification exhibiting connective tissue differentiating forming bone matrix, and moderate presence of inflammatory cells. Group AH Plus 10 (e) and 40 (f) magnification showing tissue neoformation with connective tissue filling the defect, with no sign of bone union, and moderate to intense presence of inflammatory cells.

process [6,32,33]. Release of calcium ions and high pH values were observed in a previous study evaluating the physical and chemical properties of Sealer Plus BC [6] and Bio-C Sealer [12]. During the setting process of calcium silicate-based cements, calcium ions can be released, thereby providing alkalinity to the wound microenvironment [25].

Considering the preliminary characterization of this study, the limitations include the absence of additional times points and tests like sophisticated evaluation of inflammatory cells as myeloperoxidase expression and computed tomography measurements to bone histomorphometry. However, the results obtained provide a preliminary understanding of the bone tissue behavior in contact of these two new products. Despite the short timeline evaluation their potential in promoting rapid recovery present significant results.

The degree of inflammation indicated a higher number of Sealer Plus BC-treated

samples without inflammatory cells relative to other treatment groups, which agrees with a previous study reporting little or no inflammatory response from the use of a bioceramic material [34]. Over half of the tissue slides from the Bio-C Sealer treatment group presented moderate inflammation scores. In general, the inflammatory process in tissues treated with bioceramic cements is expected during the initial repair period [21], which was included in the 15 postoperative days applied in the present study. The difference between the two bioceramic-based cements might suggest that the inflammatory process was more evident in specimens treated with the Bio-C Sealer product; however, as previously described, this factor did not interfere with tissue repair.

AH Plus sealer resulted in high inflammation values, which was in line with another study confirming the presence of an inflammatory reaction [35]. Recent reports indicated marked cytotoxic effects from freshly prepared AH Plus in vitro, with enlarged osteoblasts suggesting degeneration attributable to the resinous cement composition [36] likely causative of DNA-strand breakage and possible formaldehyde release [37]. However, acute characteristics were not present 2 weeks after sealer preparation [32], and the biocompatibility of AH Plus promoted reduced inflammation over time [38].

Sealer Plus BC and Bio-C Sealer demonstrate biocompatibility and bioactive potential in the initial repair process. Sealer Plus BC produced little or no inflammation. Bio-C Sealer caused an initial higher degree of inflammation without prejudice in bone healing process. In addition to biocompatibility and bioactivity these sealers are ready-to-use, meaning less technique steps. A follow up in longer timeline is important to a better establishment of these materials ability with accelerate tissue repair.

CONCLUSION

Sealer Plus BC and Bio-C Sealer have biocompatibility and bioactive potential superior to AH Plus in the initial bone repair process.

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Author's Contributions

MVVSC, WCA, HAS, BSF, DFF, LFF, MSCP, ASBP, MÂALF, CAMF: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing, Visualization and Supervision.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local animal subjects oversight committee guidelines and policies of: the ethics committee on the use of Animals of State University of Piauí. This study protocol was reviewed and approved by the ethics committee on the use of Animals of State University of Piauí under the approval number 0175/2018.

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