Original Research

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Effect of calcium silicate-based repair sealers on bone healing in rat skull defects: histological and histomorphometric study

Juliano Moreira Sauer[1], Carlos Eduardo da Silveira Bueno[1], Rina Andrea Pelegrine[1], Carlos Eduardo Fontana[2], Elizabeth Ferreira Martinez[1], Pedro Giorgetti Montagner[1], Wayne Martins Nascimento[1], Ana Grasiela da Silva Limoeiro[3] ✉, Daniel Guimarães Pedro Rocha[2], Marilia Fagury Videira Marceliano-Alves[4,5,6], Michelle Paiva Weydt Galhardi[7], Michel Klymus[1], Alexandre Sigrist De Martin[1]

[1] Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Campinas, São Paulo, Brazil

[2] PUC Campinas, Campinas, São Paulo, Brazil

[3] Bauru School of Dentistry, University of São Paulo, Bauru, Brazil

[4] Maurício de Nassau University Centre (UNINASSAU), Rio de Janeiro, Brazil

[5] Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil, Pune, India

[6] Post-Graduate Program in Dentistry, Iguaçu University, Nova Iguaçu, Rio de Janeiro, Brazil

[7] São José University, Rio de Janeiro, Brazil

✉ grasielalimoeiro@gmail.com

Abstract

AIM. This study investigated the impact of calcium silicate sealers on bone healing in rat calvaria defects.

MATERIALS AND METHODS. Twenty-six rats were divided into 3 groups. Calvaria defects were prepared and treated in 3 different ways: CG (n = 6): Filling with clot; ES (n = 10): Filling with Endosequence BC RRM Putty repair sealer and BC (n = 10): Filling with Bio C repair sealer.

RESULTS. After 15 and 30 days, histological evaluations revealed varied levels of bone regeneration and inflammation. The group treated with a blood clot showed more bone regeneration without inflammation at 15 days. However, after 30 days, complete closure of the defect with immature tissue was observed in this group, while limited new bone formation occurred in the other groups, accompanied by mild inflammation.

CONCLUSIONS. Overall, the study suggests that calcium silicate-based sealers can induce new bone formation, but they do not offer superior bone repair compared to natural healing with a blood clot alone.

Keywords: animal model, endodontics, dental materials.

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Влияние кальций-силикатных восстановительных цементов на заживление костной ткани при дефектах черепа у крыс: гистологическое и гистоморфометрическое исследование

Ж.М. Зауэр[1], К.Э.С. Буэно[1], Р.А. Пелегрине[1], К.Э. Фонтана[2], Э.Ф. Мартинес[1], П.Д. Монтагнер[1], У.М. Насименту[1], А.Г.С. Лимойру[3] ✉, Д.Г.П. Роша[2], М.Ф.В. Марселиано-Алвес[4,5,6], М.П.В. Галхарди[7], М. Климус[1], А.С. Мартин[1]

[1] Научно-исследовательский институт Сан-Леопольду Мандик, Кампинас, штат Сан-Паулу, Бразилия
[2] Католический университет Кампинаса (PUC Campinas), г. Кампинас, штат Сан-Паулу, Бразилия
[3] Стоматологическая школа Бауру, Университет Сан-Паулу, г. Бауру, Бразилия
[4] Университетский центр Маурисиу де Нассау (UNINASSAU), г. Рио-де-Жанейро, Бразилия
[5] Стоматологический колледж и госпиталь им. д-ра Д.Й. Патила, Университет д-ра Д.Й. Патила, г. Пуна, Индия
[6] Университет Игуасу, г. Нова-Игуасу, штат Рио-де-Жанейро, Бразилия
[7] Университет Сан-Жозе, г. Рио-де-Жанейро, Бразилия
✉ grasielalimoeiro@gmail.com

Резюме

ЦЕЛЬ. В данном исследовании изучалось влияние кальций-силикатных цементов на заживление костной ткани при дефектах свода черепа у крыс.

МАТЕРИАЛЫ И МЕТОДЫ. В исследование было включено 26 крыс, разделенных на 3 группы. Дефекты в области свода черепа создавались и обрабатывались тремя способами: CG (n = 6): заполнение сгустком крови (контроль); ES (n = 10): заполнение восстановительным цементом Endosequence BC RRM Putty; BC (n = 10): заполнение цементом Bio C Repair.

РЕЗУЛЬТАТЫ. Через 15 и 30 дней проводилась гистологическая оценка, которая показала различный уровень регенерации кости и выраженности воспаления. В группе, где применялся только кровяной сгусток, на 15-й день наблюдалась более активная костная регенерация и отсутствие воспаления. Однако через 30 дней в этой группе дефект был полностью закрыт незрелой тканью, тогда как в остальных группах формирование новой костной ткани было ограниченным и сопровождалось слабовыраженным воспалением.

ВЫВОДЫ. В целом исследование показало, что кальций-силикатные цементы способны индуцировать образование новой кости, однако не обеспечивают более эффективного восстановления костной ткани по сравнению с естественным заживлением при использовании одного лишь сгустка крови.

Ключевые слова: животная модель, эндодонтия, стоматологические материалы

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INTRODUCTION

Bioceramic sealers have been developed with the aim of making procedures such as pulp capping, pulpotomies, perforation repairs, root resorption treatments, apex formation treatments, and retrograde fillings more predictable [1]. However, the direct contact of these sealers with pulp and periodontal tissues may raise concerns regarding their biocompatibility [1]. The interaction of these materials with tissues is often suggested with the aim of promoting tissue regeneration/repair [2], but it is important to evaluate potential adverse reactions such as inflammation [3; 4].

MTA (mineral trioxide aggregate) is a material that revolutionized endodontics in the 1990s [5]. It is considered the biocompatible treatment option of choice in many cases of root perforations, internal and external resorptions, and pulp capping [6; 7]. However, MTA has some disadvantages [8], such as low compressive strength, high pigmenting power of the remaining tooth structure, time-consuming setting. Due to its low flowability, it is difficult to handle when it clumps with distilled water, resulting in a sandy appearance and making it impractical to use [6; 8; 9].

To overcome the drawbacks of MTA, new calcium silicate-based materials have been developed to improve handling, setting time, and release of heavy metals 10. These third-generation materials have been evaluated for their cytotoxicity, regenerative potential, and overall biocompatibility [4; 10–14].

Some of these sealers, such as EndoSequence Root Repair Material Putty (Brasseler USA, Savannah, GA, USA) and Bio-C Repair (Angelus, Londrina, PR, Brazil)

have been successfully applied both in vitro and in vivo [5; 7; 11; 15]. However, there is still controversy and unconvincing results compared to MTA [8; 11; 16; 17].

Although used as an adjuvant and even as the main material in various clinical situations in endodontics, several studies question their ability to form bone [18–20], an essential property within their indications.

Given the difficulty in conducting clinical trials to evaluate the efficacy of these materials, research has focused on animal models. The present study, conducted in rats, aimed to evaluate histologically and histomorphometrically the effect of calcium silicate-based repair sealers, Endosequence BC RRM Putty and Bio C Repair, on bone healing in skull defects. The null hypothesis is that there is no difference in bone healing between defects filled with clot or repair sealers.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki. Twenty-six rats of the species *Rattus norvegicus albinu*, class Mammalia, order Roedentia, of the Wister strain, were used for this study. The research was approved by the local Ethics Committee for the Use of Animals under the number 2020/13 (Date: June 30, 2020). The selected animals were young adult animals without genetic modification, approximately 3 months old and weighing 300 g each. The animals were kept in the animal house in cages lined with autoclaved wood shavings, changed daily, with three animals per cage. The environment had controlled lighting with 12 hours of light and 12 hours of darkness, a controlled temperature of 21°C, and water and food *ad libitum*.

Sample calculations were based on a critical value of 1.96 for the 95% confidence interval, a maximum acceptable variance of 0.23 (23%) based on a preliminary experiment 21 a minimum standard error of 5% of the mean, and a significance level of $p < 0.05$. The manuscript of this laboratory study was written according to the PRIASE 2021 guidelines for reporting animal studies in Endodontology.

The 26 animals were randomly divided into 3 groups, namely CG – control group with 06 animals and experimental groups ES and BC with 10 animals each according to the intervention to be performed and, divided into two groups according to the observation period of 15 and 30 days. The division of the groups can be seen in Table 1.

For surgical interventions, the animals were previously restrained and subjected to general anesthesia. For this purpose, they were injected intraperitoneally with ketamine hydrochloride (Ketamine Agener, Agener União, Embu-Garçu, Brazil) at a dose of 75mg/Kg and xylazine hydrochloride (Dopaser, Hertape Calier S.A, Juatuba, Brazil) at a dose of 10mg/Kg. After confirming effective analgesia of the animals, they were trichotomized in the calvaria region and positioned in ventral decubitus position on a special couch on which the region to be operated was immobilized. Asepsis was performed in the region of the skullcap using iodine alcohol as a local antiseptic. Then, a semilunar incision was made in the median region of the skull of the rats, followed by a wide lateral excision and exposure of the calvaria. A 4-mm-diameter trephine burr was used to drill a 1-mm-deep, circular, noncritical bone defect in the calvariae of the rats under constant irrigation with saline at low rotation. During surgery, sterile gauze soaked with 0.9% saline was placed over the animals' eyes to prevent corneal desiccation.

The defects were filled and treated as described in Table 1. The wound was then sutured with 4.0 silk suture (Ethicon, Johnson & Johnson, São José dos Campos, Brazil) to properly close the flap edges.

After surgery, the muscle relaxant tramadol was administered intraperitoneally at a dose of 5 mg/Kg every 24 hours for 3 days, in addition to the analgesic flunixin meglunin at a dose of 1.1 ml/Kg in a single dose. No anti-inflammatory or antibiotic drugs were administered preoperatively or postoperatively to allow the healing process to take its natural course.

The operated animals were routinely observed from the first surgical act (creation of the defect and insertion of the bioceramic cements) until euthanasia. Animals were euthanized 15 and 30 days after surgery by an overdose of anesthetic, according to the protocol of choice: 90–150 mg sodium thiopental (71-73-8) associated with 10 mg/ml lidocaine (137-58-6), intraperitoneally.

After euthanasia, histologic analysis was performed by conventional light microscopy of slides stained with hematoxylin and eosin. The analysis was performed by a single examiner. Grades from 0 to 3 were assigned to measure the intensity of the inflammatory infiltrate, with 0 representing an inflammatory infiltrate of up to 15%, 1 representing an infiltrate between 15 and 50%, 2 representing an infiltrate of more than 50% up to 75%, and 3 representing an infiltrate of more than 75%. Histomorphometry assessment was also performed by a single investigator who was blinded to the work performed. The total area observed was measured in square micrometers (μm2) and was considered 100%, and the bone area analyzed was its percentage relative to the total area.

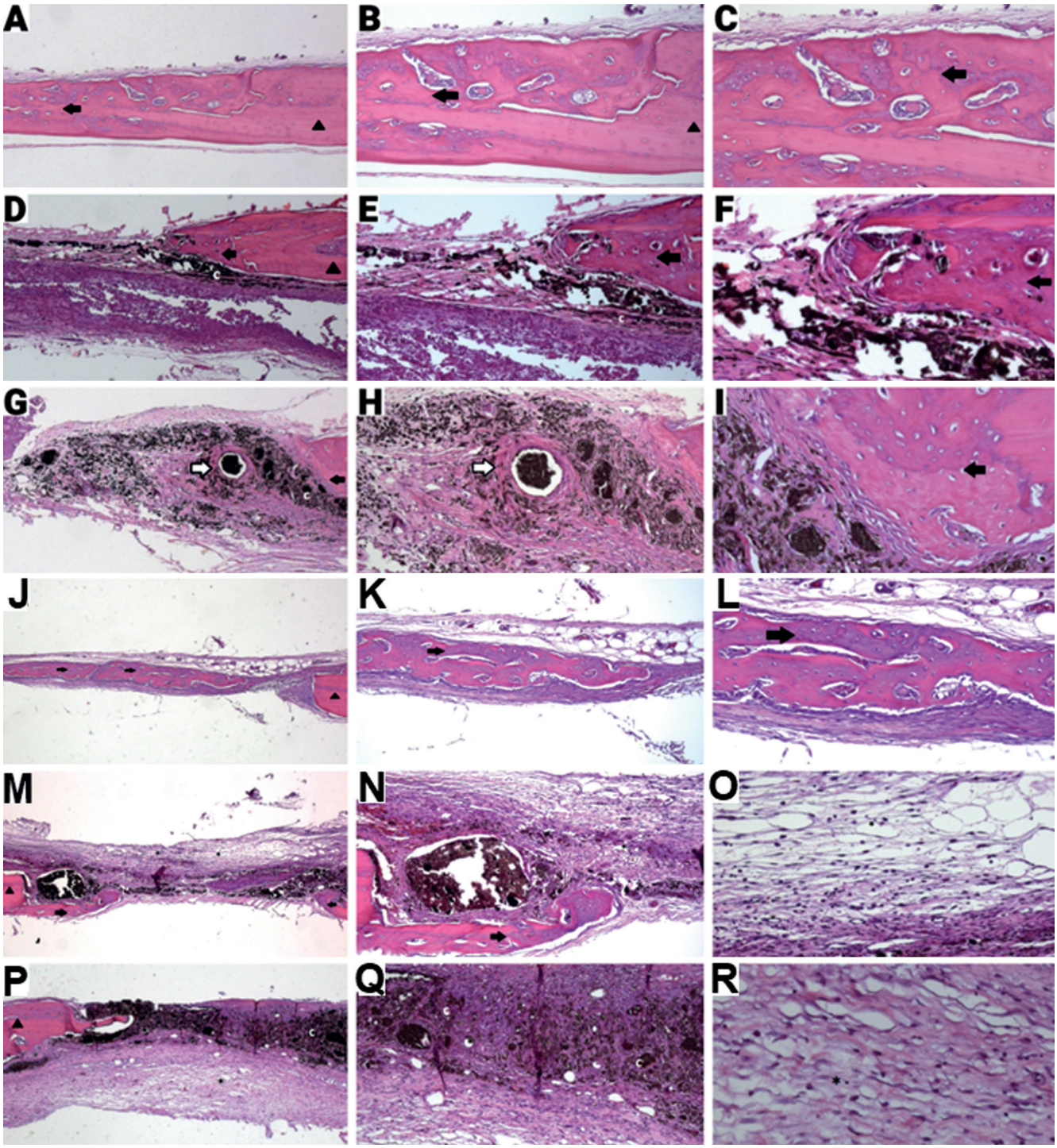
Statistical Analysis

Then, the inflammation data were statistically analyzed and subjected to Kruskal-Wallis test followed by Mann-Whitney U test with a significance level of 5%, and the histomorphometric data were subjected to descriptive statistics.

Table 1. Allocation of experimental groups

Таблица 1. Распределение экспериментальных групп

Group	N	Euthanasia	Intervention
CG	3	15 days	Animals subjected to cranial trephination without insertion of bioceramic sealer – repair with blood clot only
	3	30 days	
ES	5	15 days	Animals subject to cranial trephination using Endosequence BC RRM Putty repair sealer – Brasseler
	5	30 days	
BC	5	15 days	Animals subjected to cranial trephination using Bio C repair sealer – Angelus
	5	30 days	



Legend: ➡ area of new bone formation; ▲ mature bone; C – repair sealer; ∗ mononuclear inflammatory infiltrate; ⇨ phagocytic inflammatory giant cell

Легенда: ➡ область новообразования кости; ▲ зрелая кость; C – репарационный цемент; ∗ мононуклеарный воспалительный инфильтрат, ⇨ фагоцитирующая воспалительная гигантская клетка

Fig. 1. *A*, *B* and *C* – group GC after 15 days at 40x, 100x and 200x magnification, respectively; *D*, *E*, and *F* – group ES after 15 days at 40x, 100x, and 200x magnification, respectively; *G*, *H* and *I* – group BC after 15 days at 40x, 100x and 200x magnification, respectively; *J*, *K*, and *L* – group GC after 30 days at 40x, 100x, and 200x magnification, respectively; *M*, *N*, and *O* – group ES after 30 days at 40x, 100x, and 200x magnification, respectively; *P*, *Q* and *R* – group BC after 30 days at 40x, 100x and 200x magnification, respectively

Рис. 1. *A*, *B* и *C* – группа GC через 15 дней при увеличении 40x, 100x и 200x соответственно; *D*, *E* и *F* – группа ES через 15 дней при увеличении 40x, 100x и 200x соответственно; *G*, *H* и *I* – группа BC через 15 дней при увеличении 40x, 100x и 200x соответственно; *J*, *K* и *L* – группа GC через 30 дней при увеличении 40x, 100x и 200x соответственно; *M*, *N* и *O* –группа ES через 30 дней при увеличении 40x, 100x и 200x соответственно; *P*, *Q* и *R* - группа BC через 30 дней при увеличении 40x, 100x и 200x соответственно

RESULTS

The illustrative images of the histological sections stained with hematoxylin-eosin of the different groups of samples after 15 days are shown in Fig. 1. After 15 days, areas of new bone formation were observed at CG in the region near the recipient bed as well as in the central region of the defect. Osteoblasts outlining the bone spicules were also observed, and this region was well vascularized. No inflammatory process was observed. In the ES group, sealer areas distributed throughout the defect were observed with little new bone formation, strong vascularization, and a discrete, typically mononuclear inflammatory infiltrate. In the BC group, cementum and an inflammatory infiltrate were observed, also typically mononuclear, highly vascularized, and almost no area of new bone formation.

The illustrative images of the hematoxylin-eosin-stained histological sections of the different sample groups after 30 days are shown in Fig. 2. At CG, almost complete closure of the filled defect was observed with the presence of both immature bone tissue and lamellar bone. Little bone tissue was observed in the ES and BC groups. In the ES group, bone tissue was noted near the peripheral region of the defect. In the BC group, the presence of phagocytic inflammatory giant cells penetrating the biomaterial was also observed. In all groups, no lymphocytic or mononuclear infiltrate was observed in the defect region.

The control group had an inflammation value of zero during the 15-day observation period, while the ES and BC groups had a value of 1, representing a statistically significant difference between the control and experimental groups (p = 0.014). For the 30-day observation period, the 3 groups showed a value of 0, i.e., no statistical difference. In all groups and evaluation periods, there was no variability in the scores evaluated. When comparing time periods, the control group showed no statistical difference, and the ES and BC groups showed a statistically significant decrease in score (p = 0.004) from 1 at 15 days to 0 at 30 days.

DISCUSSION

The search for restorative materials that promote bone regeneration in endodontics is not a new topic [21]. In this study, two calcium silicate-based materials indicated for cases of root resorption, root perforations, pulpotomies, revascularization, retrograde obturation, and pulp capping were evaluated. However, the results obtained showed no significant advantage in bone regeneration compared with the control group, in which the defect in the calvaria of the rats was filled only with a blood clot. These results, while contradictory to the indications of the materials, are consistent with several other studies in the literature [8; 11; 16; 17; 21–23].

The assessment of bone regeneration through calvaria defects used in this study is considered the gold standard to test the tissue response promoted by root filling materials [16]. On the other hand, it might be ideal to make two defects in the same animal, one filled with clot and the other filled with the test material, so that each test sample is a separate control [24] Such a method was not used in this study because a separate animal served as the control group.

One aspect of these materials that has been much discussed in the literature is the setting time, and it is well known that calcium silicate-based sealers have a long setting time [17]. According to Damas et al. [17], Endosequence RRM Putty can set up to 12 hours in a 100% humidity and 37°C environment, but in their study, there was no complete set and evaluations at 24,

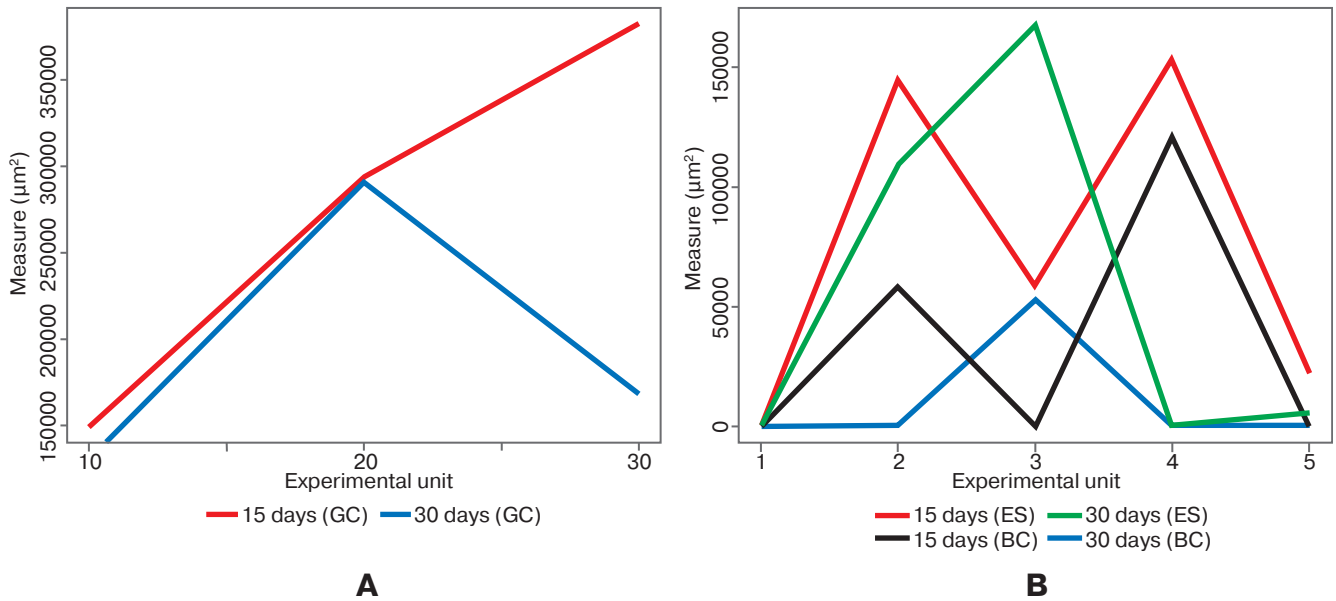


Fig. 2. Amount of newly formed bone per animal, in µm², after 15 and 30 days:
A – for the control group; *B* – for the groups ES and BC

Рис. 2. Объем новообразованной кости на животное (в мкм²) через 15 и 30 дней:
A – в контрольной группе; *B* – в группах ES и BC

72 and 120 hours. Complete setting was observed only after 168 hours. This aspect could be one of the reasons for the greater presence of an initial inflammatory infiltrate and a delay in bone regeneration [4; 13; 14].

In a previous study [25], after a 2-week treatment with AH Plus endodontic sealer, a moderate inflammatory reaction was observed, which decreased only after 4 weeks, confirming our study, in which a decrease in the inflammatory process was also observed throughout the evaluation period. However, it is worth noting that the material tested in that study was based on epoxy resin, which is significantly different from the material used in the present study. In our study, although the inflammatory process was more persistent than in the control group at the end of the observation period, the absence of a lymphocytic or mononuclear infiltrate is indicative of the biocompatibility of the sealers tested. This result is also consistent with another study [23], in which two sealers (AH Plus and Sealer Plus) were tested on calvarial hill defects in rats. In this study, the sealers caused an intense inflammatory response but were considered biocompatible because they allowed bone repair. It should also be noted that endodontic defects are usually smaller than those created in this study, resulting in less contact between the exposed material and the tissue, which could also lead to a lower inflammatory response.

The assessment of inflammation in our study was semiquantitative by initial qualitative assessment followed by quantitative assessment by scores. It is known that this type of assessment may not be accurate enough to compare different materials or different time intervals [16]. On the other hand, a purely quantitative score in this type of analysis usually shows differences only when the studied groups are very different, as it may inadequately capture small differences [16].

Finally, small differences between the sealers studied can be explained by possible differences in their surface properties, which are directly related to their biological properties. The presence of calcium in the composition of these sealers may be similar but released to the medium to different extents [3]. The release of calcium from the sealer into the medium is the main agent for cementoblast differentiation and dentin bridge formation and plays an important role in antimicrobial activity [3; 13; 14].

A recent study, also using an animal model (Wistar rats) [14], investigated eight calcium silicate-based sealers, quantifying volume change, biocompatibility, and systemic migration of sealer components using different evaluation methods. The study used sealers in powder/liquid and “ready-to-use” presentations, employing computed microtomography to assess volume variation and histological analysis to determine biocompatibility after 30 days of implantation in alveolar bones and subcutaneous tissues. Mass spectrometry was used to measure the accumulation of metals such as bismuth, tantalum, tungsten, and zirconium in the kidneys after the euthanasia of the animals. The results revealed that Biodentine, EndoSequence BC RRM Putty, and ProRoot MTA maintained better volumetric stability, although ProRoot MTA and MTA Repair HP showed metal accumulation in the kidneys. The analysis concluded that Bio-C Repair, NeoPUTTY, and MTA Repair HP lose volume in subcutaneous tissues more than in bones, with NeoPUTTY inducing more inflammation. The study suggests that the chemical composition of the sealers and the type of tissue significantly affect their clinical performance.

A limitation of this study is the use of animal model, so caution is advised during the results interpretation, due to the translation from a laboratory and in vivo study using an animal model to the patients could be distant. Further studies are needed to confirm not only the bone repair indication of calcium silicate sealers, but also the other indications that were not investigated in this study.

CONCLUSION

Within the limitations of the present study, it was found that calcium silicate-based sealers are materials that have biocompatibility properties and can enable the regeneration process in the defects in the calvaria of rats. However, compared to the control group, which was only filled with blood clots, they did not show superiority in accelerating this regeneration.

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INFORMATION ABOUT THE AUTHORS

Juliano Moreira Sauer – Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, SP, Brazil; https://orcid.org/0009-0000-7579-5117

Carlos Eduardo da Silveira Bueno – Dentist, MSc, Phd and Professor, Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, São Paulo, Brazil; https://orcid.org/0000-0002-2675-0884

Rina Andrea Pelegrine – Dentist, MSc, Phd and Professor in the Department of Endodontics, Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, São Paulo, Brazil; https://orcid.org/0000-0003-4175-2121

Carlos Eduardo Fontana – Dentist, Professor, Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, São Paulo, Brazil; https://orcid.org/0000-0002-2868-6839

Elizabeth Ferreira Martinez – Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, SP, Brazil; https://orcid.org/0000-0002-4991-1185

Pedro Giorgetti Montagner – Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, SP, Brazil; https://orcid.org/0000-0002-7836-7131

Wayne Martins Nascimento – Dentist, MSc, Phd and Professor and Researcher Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, São Paulo, Brazil; https://orcid.org/0000-0003-4201-4710

Ana Grasiela da Silva Limoeiro – Dentist, MSc, Phd and Professor, Department of Dentistry, Endodontics and Dental Materials, Bauru Dental School, University of Sao Paulo, Bauru, Brazil; https://orcid.org/0000-0003-4633-720X

Daniel Guimarães Pedro Rocha – Dr. Sc. (Med.), Lecturer and Researcher in the Department of Endodontics at the Faculty of Dentistry, PUC Campinas, Department of Endodontics, Center of Life Sciences, Programa de pós-graduação em Ciências da Saúde, Campinas, São Paulo, Brazil; https://orcid.org/0000-0001-9792-2260

Marilia Fagury Videira Marceliano-Alves – Dentist, Holds MSc and PhD degrees in Endodontics, Professor and Researcher, Professor at Posrgraduate Program in Dentistry, Iguaçu University, Nova Iguaçu, Brazil; https://orcid.org/0000-0002-2917-5934

Michelle Paiva Weydt Galhardi – Professor at Postgraduate Program in Dentistry, Iguaçu University, Nova Iguaçu, Brazil; Postgraduate Program in Dentistry, Iguaçu University, Nova Iguaçu, Brazil; Maurício de Nassau University Centre (UNINASSAU), Rio de Janeiro, Brazil; Department of Dental Research Cell, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pune, India; https://orcid.org/0009-0007-0625-2742

Michel Klymus – Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, SP, Brazil; https://orcid.org/0000-0001-6429-7964

Alexandre Sigrist De Martin – Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Department of Endodontics, Campinas, SP, Brazil; https://orcid.org/0000-0002-3320-9172

ИНФОРМАЦИЯ ОБ АВТОРАХ

Жулиано Морейра Зауэр – факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0009-0000-7579-5117

Карлос Эдуарду да Силвейра Буэно – врач-стоматолог, профессор, Faculdade São Leopoldo Mandic, Институт исследований São Leopoldo Mandic, кафедра эндодонтии, Кампинас, Сан-Паулу, Бразилия; https://orcid.org/0000-0002-2675-0884

Рина Андреа Пелегрине – доктор философии, преподаватель кафедры эндодонтии, Faculdade São Leopoldo Mandic, Институт исследований São Leopoldo Mandic, кафедра эндодонтии, Кампинас, Сан-Паулу, Бразилия; https://orcid.org/0000-0003-4175-2121

Карлос Эдуардо Фонтана – врач-стоматолог, профессор, Факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0000-0002-2868-6839

Элизабет Феррейра Мартинес – факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0000-0002-4991-1185

Педру Джорджетти Монтагнер – факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0000-0002-7836-7131

Уэйн Мартинс Насименту – врач-стоматолог, преподаватель и исследователь, Faculdade São Leopoldo Mandic, Институт исследований São Leopoldo Mandic, кафедра эндодонтии, Кампинас, Сан-Паулу, Бразилия; https://orcid.org/0000-0003-4201-4710

Ана Гразиэла да Силва Лимойру – врач-стоматолог, магистр в области эндодонтии, кафедра стоматологии, эндодонтии и стоматологических материалов, Стоматологическая школа в Бауру, Университет Сан-Паулу, Бауру, Бразилия; https://orcid.org/0000-0003-4633-720X

Даниэль Гимарайнс Педру Роша – д.м.н., преподаватель и исследователь кафедры эндодонтии стоматологического факультета Университета PUC Campinas, кафедра эндодонтии, Центр наук о жизни, программа последипломного образования по наукам о здоровье, Кампинас, Сан-Паулу, Бразилия; https://orcid.org/0000-0001-9792-2260

Марилия Фагури Видейра Марселиану-Алвес – врач-стоматолог, имеет степени магистра и доктора философии (MSc и PhD) в области эндодонтии, преподаватель и исследователь, профессор программы последипломного образования по стоматологии, Университет Игуасу (Iguaçu University), Нова-Игуасу, Бразилия; https://orcid.org/0000-0002-2917-5934

Мишель Паива Вейдт Галхарди – профессор программы последипломного образования по стоматологии, Университет Игуасу (Universidade Iguaçu), Нова-Игуасу, Бразилия; Университетский центр Маурисиу ди Нассау (UNINASSAU), Рио-де-Жанейро, Бразилия; отдел клеточных стоматологических исследований, стоматологический колледж и больница д-ра Д.Й. Патила, Видьяпит д-ра Д.Й. Патила, Пуна, Индия; https://orcid.org/0009-0007-0625-2742

Мишель Климус – факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0000-0001-6429-7964

Александр Сигрист Ди Мартин – факультет Сан-Леопольду Мандик, Научно-исследовательский институт Сан-Леопольду Мандик, кафедра эндодонтии, Кампинас, штат Сан-Паулу, Бразилия; https://orcid.org/0000-0002-3320-9172

AUTHOR'S CONTRIBUTION

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