Original scientific paper

UDK 541.123.25:631.414
DOI 10.7251/COMEN2401104J

COMPARATIVE ANALYSIS OF SUBCUTANEOUS CONNECTIVE TISSUE RESPONSES TO CALCIUM ALUMINATE AND NANOSTRUCTURED TRICALCIUM SILICATE NANOMATERIALS IN MOUSE MODELS

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Abstract: This study aimed o evaluate connective tissue reaction to experimental nanomaterial based on calcium aluminate (*ALBO-CA*) and commercial nanostructured tricalcium silicate DiaRoot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada) in Wistar rats.The study included 36 rats aged from 10 to 11 weeks. In all animals, an incision took place on the back and two pockets of 15 mm in depth were made, in which sterile polyethylene tubes with test materials (*ALBO-CA -Group F*, Diaroot Bioaggregat-Group C) were implemented. The empty half of the tubes represented a negative control. After 7, 15, and 30 days (n=12), the animals were euthanized, and the tissues were processed for histological evaluation using hematoxylin-eosin (H&E) staining. Patohystological analysis included: inflammation, bleeding, fibrous capsule, and tissue integrity around the implanted material. Data were analyzed by the Mann -Whitney U test.ALBO-CA induced a statically significantly less inflammatory response after 15 (U=42.000, Z=-2.460, p=0.014) and after 30 days (U=42.000, Z=-2.198 p=0.028). At the end observation period significantly less vascular congestion (U=42.000, Z=-2.460, p=0.014) and significantly greater preservation of connective tissue integrity was noted (U =36.000, Z=-2.769, p=0.006) after ALBO-CA implantation compared to Diaroot Bioaggregate. There were no statistically significant difference in the fibrous capsule formation between the tested materials across all observation periods. The tested materials proved to be biologically acceptable, with the experimental nanostructured ALBO-CA showing a slightly better tissue response after subcutaneous implantation in rats.

Keywords: biocompatibility, nanostructured calcium aluminates, Diaroot Bioagregate, subcutaneous connective tissue.

1. INTRODUCTION

Mineral Trioxide Aggregate (MTA) is one of the most common materials in endodontics. Since its introduction, MTA has been used as a root-end filling material, to repair root perforations, in apical plugs, and in filling root canals [1]. The documented biocompatibility and bioactivity serve tounderscore its significance [2], highlighting its importance in clinical applications. After interaction with phosphate-buffered saline (PBS), MTA was able to induce hydroxyapatite or carbonated apatite formation [3,4]. After implantation into the subcutaneous tissue of rats, it stimulated the formation of calcite crystals and a layer of mineralized tissue confirming the material's bioactivity [3,4,5]. Despite its satisfactory biological characteristics, MTA has several drawbacks, such as reduced working time, long setting time, and difficulty of use in the filling of root canals [6,7]. In recent decades, research has been carried out to find materials that would retain the good and overcome the bad characteristics of the MTA [8-13].

One such material is Diaaroot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada) Diaaroot Bioaggregate (BA) presents the first commercial nanostructured cement based on tricalcium silicate. It contains about 41% tricalcium silicate, and tantalum oxide is included as a contrast agent. The manufacturer claims that DiaRoot is produced under controlled conditions to form contamination-free biocompatible ceramic nanoparticles (DiaRoot; DiaDent, Burnaby, BC, Canada). It is the first nanoparticulate repair cement introduced on the dental market. It is claimed that BA promotes cementogenesis and forms a hermetic seal. MTA and BA have similar compositions and uses. The most significant difference between these two products is that BA is aluminum-free [8,13-15]. The material showed biocompatibility comparable to MTA, and according to the results of one study, it does not have a toxic effect on human pulp and periodontal ligament cells [16].

In recent years, there has been a growing interest in calcium aluminate cement and the possibilities of its application in endodontics [17]. Recently, non-commercial new nanomaterials based on calcium aluminate have been synthesized, according to the original recipe of *V. Jokanović* [9].

For these materials to be used routinely in dental practice, research evaluating their biocompatibility must be conducted. Subcutaneous implants in rats are often used to evaluate the biological compatibility of various dental materials. The advantage of subcutaneous implantation into animal tissue is the simplicity, reliability, and precision of the method [9,18-20].

This study aimed o evaluate connective tissue reaction to experimental nanomaterial based on calcium aluminate (*ALBO-CA*) and commercial nanostructured tricalcium silicate DiaRoot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada) in Wistar rats.

2. MATERIAL AND METHODS

The study was conducted in the vivarium of the Faculty of Natural Sciences and Mathematics in Banja Luka, after obtaining the consent of the Ethics Committee of the University Clinical Center in Banja Luka, number 01-9-192.2/15, Bosnia and Herzegovina.

2.1. Tested Materials

Experimental nanostructured biomaterial based on calcium aluminate (CA) was compared with commercial nanostructured tricalcium silicate DiaRoot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada), which was used as a control.

Nanostructured biomaterial based on calcium aluminate (CA) was synthesized according to the method of Professor Jokanović and his associate using new technology, a combination of the hydrothermal sol-gel method and the method of self-combusting waves. Tested material ($CaO \bullet Al_2O_3 + CaCO_3 + Bi_2O_3$) was obtained by mixing $CaCO_3$, Bi_2O_3, and $BaSO_4$ with calcium-aluminate phase in a ratio of 2: 2: 1. To obtain calcium aluminate endodontic mixtures, it was necessary first to synthesize particular components of the mixture: calcium aluminate (CaO•Al2O3, CA) and calcite (CaCO3). The mixture was finally mixed with distilled water in a ratio of powder/water 2: 1, to achieve the consistency of cement paste.

The composition of DiaRoot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada) is tricalcium silicate, dicalcium silicate, tantalum pentoxide, and calcium phosphate monobasic. To provide radiopacity, tantalum pentoxide is used in BA rather than the bismuth oxide used in MTA [8,14,15].

2.2. Design ff the Study

The animal model was rats of the Wistar strain (36 rats, aged from 10 to 11 weeks, with average weight from 190 to 280 g). During the experiment rats had free access to food and water, a 12-hour shift of light and dark, air temperature ranged from 20 to 23 °C, and humidity 60% ± 10%. Depending on the implanted material rats were divided into two experimental groups: C (a group with implanted Bioaggregate) and F (a group with implanted ALBO-CA). 12 rats were sacrificed after 7, 15, and 30 days. Subcutaneous implantation of polyethylene tubes (length 10 mm, inner diameter 1 mm) was conducted, up to half filled with tested materials (Bioagregate-C group, ALBO-CA -F group,) and half empty. The empty half of the tube was a negative control. Two tubes were placed on the back of each rat, on the right side of the tube with ALBO- CA, and on the left side of the spinal column of the tube with the Bioagregate (positive control). Tubes were oriented so that the material was always turned to the head, and the empty part of the tube to the tail. Before the surgical procedure, rats were introduced to general anesthesia (Ketamin 90 mg/kg body weight, Ketamine Hydrochloride Injection USP Rotexmedica-Germany in combination with Xylazine 5 mg/kg body weight 2% Xylazine, Cp Pharma, Bergdorf, Germany).

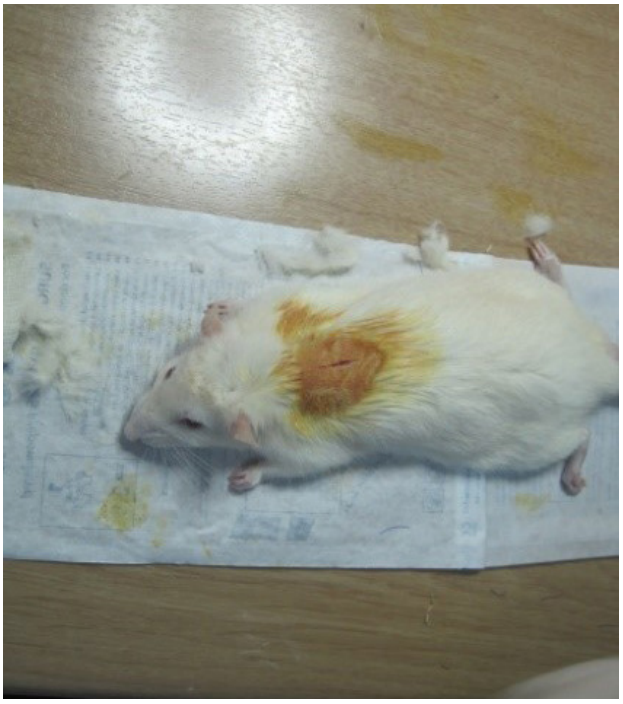

Figure 1. *Prepared operational field with an incision made*

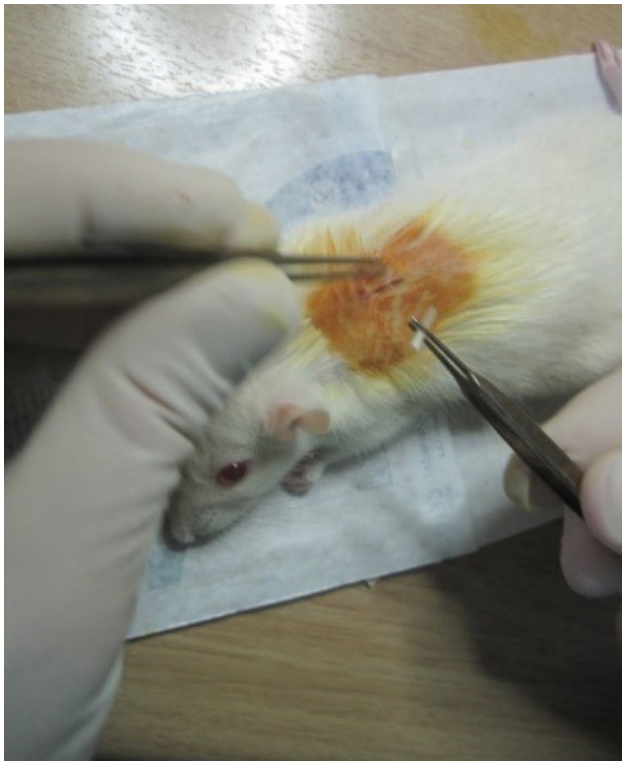

Figure 2. *Implantation of the test tub material into the subcutaneous tissue of rats*

Preparation of the operational field was carried out, and then a blunt dissection, right and left of the spinal column, two pockets of depth about 15 mm were formed. Sterile polyethylene tubes, previously filled with freshly mixed test materials, are placed in the pockets in this way. After that, the wound was sewn. An individual knotted seam was applied. After the operation animals were placed in one cage in a controlled environment, with a controlled diet and daily professional care. Animal health control was carried out three times a day. Twelve animals were sacrificed in each observation period (7, 15, and 30 days). For this purpose, an intravenous injection of Pentobarbital (Pentobarbital sodium salt 100 mg /ml, Sigma-Aldrich Chemie GmbH, Steinheim, Germany) was used.

Prepared subcutaneous tissue, together with tubes, was immersed in 10% formalin and delivered to laboratories for histological analysis. For histological analysis, 4 samples were taken from each animal. After that, tissue clip fixation together with polyethylene tubes was performed in 10% buffered formalin, paraffin molding, and paraffinic dyeing (4 μm thickness) of hematoxylin-eosin (HE).

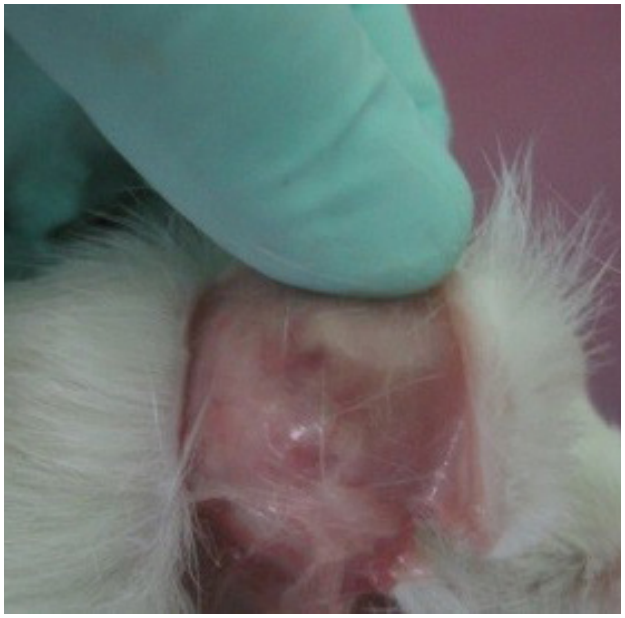

Figure 3. *Polyethylene tube in the subcutaneous tissue of rats*

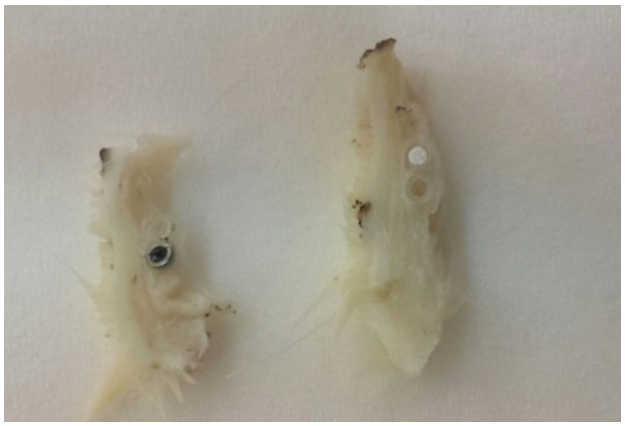

Figure 4. *a) and b) Subcutaneous tissue samples with polyethylene tubes*

Analysis of the preparation was done on a light microscope (Olympus BX-51, Japan) by an experienced pathologist, who did not participate in the sampling of the material. Histological analysis of the prepared samples was performed qualitatively and semiquantitative, and the inflammatory reaction, vascular congestion, fibrous capsule, and the preservation of the integrity of the connective tissue were considered.

2.3. Statistical Analysis

The Mann-Whitney U test was used for statistical analysis of the obtained results of subcutaneous implantation in rat tissue. Mann-Whitney U test is the non-parametric alternative test to the independent sample t-test. It is a non-parametric test that is used to compare two sample means that come from the same population, and used to test whether two sample means are equal or not.

3. RESULTS

The results of the histological analysis are shown in Tables 1, 2, and 3. After a 7-day histopathological analysis in subcutaneous tissue samples with ALBO-CA in 10 cases (83.3%) a moderate inflammatory reaction was recorded, while in 2 cases (16.7%) it was assessed as pronounced. In the same observation period, in samples with Bioaggregate, a moderate inflammatory reaction was found in 9 (75.0%) cases, and pronounced in 3 (25.0%) cases. There was no significant difference in the inflammatory reaction between the materials in this period. Moderate inflammation was traced by moderate vascular congestion in 8 samples with ALBO-CA (66.7%) and 6 samples with Bioaggregate (50.0%), while in 4 ALBO-CA samples (33.3%) and 6 Bioaggregate samples (50.0%) it was assessed as pronounced with by rupture of a blood vessel, without a statistically significant difference. In both examined materials, the fibrous capsule was completely absent in 7 cases (58.3%) while in 5 cases it was minimal (41.7%). Minimal damage to the connective tissue structure was found in all 12 samples (100.0%) of both tested materials. In the control preparations, 7 days after subcutaneous implantation, the presence of moderate intensity inflammatory reaction, and one case of pronounced inflammatory reaction in the control of the ALBO-CA material. Blood ves-

sels showed signs of moderate vascular congestion, which was more expressed in the control group of Bioagregate. In all control preparations, there was a moderate disturbance of connective tissue structure. The fibrous capsule was absent in all control preparations of ALBO-CA, and Bioagregate.

After 15 days, in all 12 samples with ALBO-CA, a mild inflammatory reaction was recorded, while in the samples with Bioaggregate, there were 7 (58.3%) cases with a mild and 5(41.7%) cases with a moderate inflammatory reaction with a statistically significant difference (U= 42.00, Z= -2.460, p=0.014). Vascular congestion was mild in 7 samples with ALBO-CA (58.3%) and 6 samples (50.0%) with Bioaggregate, while in the rest of the samples of both tested materials, the bleeding was moderate, without significant difference. During this observation period, the fibrous capsule was thin (83.3% ALBO-CA samples, 91.7% Bioagregate samples) or moderately thick (16.7% ALBO-CA samples, 8.3% Bioagregate samples), with no significant difference between materials. After 15 days, a slight deterioration of the connective tissue structure was recorded in all 12 samples (100.0%) of both tested materials. In control preparations after 15 days, a weaker inflammatory response was recorded in ALBO-CA control while control preparations for Bioagregate were rated as moderate inflammatory response. In all control preparations, a slight disturbance of the structure of the loose connective tissue was observed, followed by the formation of a thin fibrous capsule. Vascular congestion was equally expressed in the control group of ALBO-CA and Bioaggregate.

At the end of the observation period, after 30 days, in as many as 50% of samples with ALBO-CA, inflammation was completely absent, while in the other 50%, a minimal inflammatory reaction was recorded. After 30 days of subcutaneous implantation of Bioaggregate, 1 sample (8.3%) without inflammation was recorded, while in 11 (91.7%) samples the inflammatory reaction was minimal. This difference was statistically significant (U = 42.000, Z = -2.198, p = 0.028). In ALBO-CA samples, the complete absence of bleeding was found in 5 cases (41.7%), while in the other 7 cases (58.3%) minimal bleeding was noted. In tissue samples with Bioaggregate, minimal bleeding with statistically significant difference (U = 42.000, Z = -2.460, p = 0.014). The fibrous capsule became moderately thick in 9 samples with ALBO-CA (75.0%) and 8 samples with Bioaggregate (66.7%), and thick in 3 samples with ALBO-CA (25.0%) and 4 samples with Bioaggregate (33.3%). Better preservation of connective tissue integrity was found after subcutaneous implantation of ALBO-CA where complete preservation of structure was recorded in 6 samples (50.0%), while after application of Bioaggregate in all 12 samples (100.0%) minimal deterioration of connective tissue structure was found. This difference was highly statistically significant (U = 36.000, Z = -2.769, p = 0.006). In control preparations after 30 days, a weaker inflammatory response, lower vascular congestion, and better integrity of the binders were observed in control samples of ALBO-CA compared with Bioagregate. A moderately thick or thick fibrous capsule was formed thicker in the control of ALBO-CA material.

Table 1. *Analyzed parameters after 7 days of implantation into rat subcutaneous tissue*

			Inflammatory reaction after 7 days		Total	Vascular congestion 7 days		Total	Fibrous capsule 7 days		Total	Disturbance of connective tissue structure	Total
			moderate	pronounced		moderate	pronounced		absent	minimal		moderate	
Group	C	N	9	3	12	6	6	12	7	5	12	12	12
		%	75.0%	25.0%	100.0%	50.0%	50.0%	100.0%	58.3%	41.7%	100.0%	100.0%	100.0%
	F	N	10	2	12	8	4	12	7	5	12	12	12
		%	83.3%	16.7%	100.0%	66.7%	33.3%	100.0%	58.3%	41.7%	100.0%	100.0%	100.0%
Total		N	19	5	24	14	10	24	14	10	24	24	24
		%	79.2%	20.8%	100.0%	58.3%	41.7%	100.0%	58.3%	41.7%	100.0%	100.0%	100.0%

Table 2. *Analyzed parameters after 15 days of implantation into rat subcutaneous tissue*

			Inflammatory reaction after 15 days		Total	Vascular congestion after 15 days		Total	Fibrous capsule after 15 days		Total	Disturbance of connective tissue structure	Total
			mild	moderate		mild	moderate		thin	Moderately thick		treasure	
Group	C	N	7	5	12	6	6	12	11	1	12	12	12
		%	58.3%	41.7%	100.0%	50.0%	500%	100.0%	91.7%	8.3%	100.0%	100.0%	100.0%
	F	N	12	0	12	7	5	12	10	2	12	12	12
		%	100.0%	0.0%	100.0%	58.3%	41.7%	100.0%	83.3%	16.7%	100.0%	100.0%	100.0%
Total		N	19	5	24	13	11	24	21	3	24	24	24
		%	79.2%	20.8%	100.0%	54.2%	45.8%	100.0%	87.5%	12.5%	100.0%	100.0%	100.0%

Table 3. *Analyzed parameters after 30 days of implantation into rat subcutaneous tissue*

			Inflammatory reaction after 30 days		Total	Vascular congestion after 30 days		Total	Fibrous capsule after 30 days		Total	Preservation of connective tissue integrity for 30 days		Total
			absent	minimal		absent	minimal		Moderately thick.	thick		completely	minimal structural disturbance	
Group	C	N	1	11	12	0	12	12	8	4	12	0	12	12
		%	8.3%	91.7%	100.0%	0.0%	100.0%	100.0%	66.7%	33.3%	100.0%	0.0%	100.0%	100.0%
	F	N	6	6	12	5	7	12	9	3	12	6	6	12
		%	50.0%	50.0%	100.0%	41.7%	58.3%	100.0%	75.0%	25.0%	100.0%	50.0%	50.0%	100.0%
Total		N	7	17	24	5	19	24	17	7	24	6	18	24
		%	29.2%	70.8%	100.0%	20.8%	79.2%	100.0%	70.8%	29.2%	100.0%	25.0%	75.0%	100.0%

4. DISCUSSION

Biocompatibility tests are used to detect components of the material that could cause injuries or damage to the tissues of the oral cavity or the organism in general. Adverse tissue reactions may be due to the toxicity of the applied material, but also to other factors, such as the accumulation of infectious material. Biocompatibility tests are performed in vitro and in vivo [21]. In vivo, biocompatibility tests involve experimental research on animals or on patients who have voluntarily consented to such cooperation. The most common animals in dental experiments are without a doubt rats. The first written record of experimentation in rats dates back to the mid-19th century when Philipeaux studied how adrenalectomy affected albino rats. The first rats bred for medical testing were at the Wistar Institute in Philadelphia [22, 23]. There are many reasons why we, and many researchers before us, opted for these experimental animals. Among other things, there are accessibility, economy, the impossibility of vomiting, and exceptional adaptation to life in the laboratory.

Subcutaneous implants in rats are often used to evaluate the biological compatibility of various dental materials. The advantage of subcutaneous implantation into animal tissue is the simplicity, reliability, and precision of the method [9,18-20].

To methodologically assess the reaction of subcutaneous tissue of rats to implanted materials, histological analysis was applied, which included the degree of inflammatory reaction, bleeding, assessment of preservation of connective tissue structure, and thickness of fibrous capsule around implants, as one of the most important factors confirming biocompatibility of materials.

Taking into account the simplified sterilization, inertness, and wide use, polyethylene tubes were used in the experiment [9,12].

More intensive research on calcium aluminate cement in the past ten years has been the impetus for the synthesis of nanostructured calcium aluminate cement called ALBO-CA [24,25]. Previous studies that have investigated this experimental material have shown good, encouraging results. Mechanical investigations showed a very high compressive strength of ALBO-HA after 28 days of hydration (94MPa) and a relatively short setting time (2h) [26]. Biological investigations when applying the MTT test on the human line of human fibroblasts (MRC-5) showed a cytocompatible effect of ALBO-CA comparable to commercial calcium aluminate cement EndoBinder (Binder, São Carlos, SP, Brazil) [11] and the material also showed the absence of genotoxic potential when applying the Comet test [26]. n addition, a previous study by *Janković et al.* of the subcutaneous tissue of rats showed good tolerance of calcium aluminate nanostructured biomaterials and comparable to nanostructured calcium silicate ALBO-CSHA and commercial calcium silicate cement (MTA) [9].

Since this is a material that is still in the phase of experimental and preclinical studies, we decided to examine the reaction of subcutaneous tissue of rats to the implantation of this nanomaterial in comparison with Diaaroot Bioaggregate (DiaDent Group International, Burnaby, BC, Canada) the first commercial nanostructured cement based on tricalcium silicate.

According to the results obtained by this study, the tissue around the tested materials or empty tubes (negative control) showed the highest level of inflammation in the first 7 days, which is in line with the findings of some other researchers [9,12,27] who explain a slightly more pronounced initial inflammatory response to implantation. by the reaction to the surgical implantation procedure, by the initial adaptation of the tissue to the implanted material as well as by the stimulation of inflammatory cytokines. With time, a decrease in the intensity of inflammation was noted, with an increase in the thickness of the fibrous capsule in both tested materials.

ALBO-CA induced a smaller inflammatory response after 15 and after 30 days, less vascular congestion, and less connective tissue damage compared to Diaroot Bioaggregate. The higher bioactivity of this material is possibly related to the chemical nature of the material and the method of its synthesis. The nanostructured calcium aluminate biomaterial, tested in this study, was produced by a combination of two methods: the hydrothermal sol-gel method and the wave self-combustion method. According to the data in the literature, the materials obtained by sol-gel methods are more bioactive than those obtained by other synthetic methods.

If we exclude the previously mentioned study by *Janković et al. (2018)* in which this material confirmed a good although comparable tissue response with experimental CS and MTA, to our knowledge no other tests of this material were performed by subcutaneous implantation [9].

Three studies *(Garcia et al, Aguilar et al, Aminozarbian et al,.)* were performed in which the biocompatibility of commercial and experimental calcium aluminate cement by subcutaneous implantation was assessed [18, 19, 28].

Consistent with our results for the investigated experimental calcium aluminate cement is a study by *Aguilar et al. (2012)* that recorded a better response of rat tissue to the implantation of commercial calcium aluminate cement Endobinder compared to MTA. This result is explained by the way of synthesis of EndoBinder, primarily by the phase with low Ca content, which leads to the release of a smaller amount of calcium ions, making it more tolerable and cytocompatible with tissues [19].

In two other studies *(Garcia 2014. and Aminozarbian 2012.)* calcium aluminate cement: Endobinder and a mixture of wollastonite and calcium aluminate cement WOLCA showed no inflammation and a significant increase in fibrous capsule thickness after 30 days of subcutaneous implantation, but tissue reaction. was similar to the MTA. *Aminozarbian et al.* believe that the addition of 5% Na-HMP dispersant to the tested calcium aluminate cement adversely affects biocompatibility while *Garcia et al.* find an explanation in a different methodology [18, 28].

Interestingly, there was no significant difference in the thickness of the fibrous capsule around the ALBO-CA implants and the Bioaggregates examined by this study, which certainly speaks in favor of the biological acceptability of both tested materials.

Our result for Bioagregat is in line with the findings of *Bosia et al (2014.)* where even after 90 days of subcutaneous implantation in rat tissue, Bioagregat proved to be biologically acceptable [8].

Simsek et al (2015.) assessed tissue inflammation caused by three endodontic repair materials: micro mega-Mineral trioxide aggregate (MM-MTA), Bioaggregate (BA), and Biodentin (BD), which are incorporated into rat subcutaneous tissue. MM – MTA, and BA showed similar biocompatibility. At the end of the observation after day 45, there was no difference between MM - MTA, BA, and BD and in this study, BA also used suitable materials for endodontic repairs [29].

In a study by *Batur et al,* DiaRoot BioAggregate showed significantly better results and greater biocompatibility than MTA, after subcutaneous implantation into rat tissue after 90 days [30].

On the other hand in a study by *Saghiri et al. (2013.)* at the end of the observation after 60 days, the obtained results are contradictory. The Angelus-MTA group showed no significant differences compared to the Bioaggregate group ($P = 0.15$); however, ProRoot WMTA caused significantly less inflammation than bioaggregates ($P = 0.02$) [5].

Based on previous knowledge of the Bioaggregate, it is clear that it is a biocompatible material, and different results in various studies are associated with the application of different methodological assessments, experimental conditions, and different observation periods because although the efficiency of animal tests is higher than in vitro studies it is difficult to monitor control variables.

5. CONCLUSION

The tested materials proved to be biologically acceptable, with the experimental nanostructured ALBO-CA showing a slightly better tissue response after subcutaneous implantation in rats. The biocompatibility of this nanomaterial should be checked in other experimental studies before clinical use on the human population.

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КОМПАРАТИВНА АНАЛИЗА ОДГОВОРА ПОТКОЖНОГ ВЕЗИВНОГ ТКИВА НА КАЛЦИЈУМ АЛУМИНАТ И НАНОСТРУКТУРНЕ ТРИКАЛЦИЈУМ СИЛИКАТНЕ НАНОМАТЕРИЈАЛЕ НА МОДЕЛУ МИША

Сажетак: Циљ ове студије је био да се процијени реакција везивног ткива на експериментални наноматеријал на бази калцијум-алумината (ALBO-CA) и комерцијални наноструктурни трикалцијум-силикат DiaRoot Bioaggregat (DiaDent Group International, Burnaby, BC, Canada)) код пацова соја Wistar. Студија је обухватила 36 пацова старости од 10 до 11 недеља. Код свих животиња начињен је рез на леђима и формирана два џепа дубине 15 mm у која су аплициране стерилне полиетиленске тубице са испитиваним материјалима (ALBO-CA -Група Ф, DiaRoot Bioaggregat -Група Ц). Празна половина тубица је представљала негативну контролу. После 7, 15 и 30 дана (n=12), животиње су еутаназиране, а ткива обрађена за хистолошку анализу примјеном хематоксилин-еозин бојења. Патохистолошка анализа је обухватала: запаљење, крварење, фиброзну капсулу и интегритет ткива око уграђеног материјала. Подаци су анализирани Mann Whitney U тестом. ALBO-CA је индуковао статистички значајно мањи инфламаторни одговор после 15 (U = 42,000, Z = -2,460, p = 0,014) и после 30 дана (U = 42,000, Z = -2,198 p = 0,028,). На крају периода посматрања примијећена је знатно мања васкуларна конгестија (U = 42.000, Z = -2.460, p = 0,014) и значајно веће очување интегритета везивног ткива (U = 36.000, Z = -2.769, p = 0,006) након ALBO-CA имплантација у поређењу са DiaRoot Bioaggregatom. Mann Whitney U тест није показао статистички значајну разлику у дебљини фиброзне капсуле између испитиваних материјала у било које контролно вријеме. Тестирани материјали су се показали биолошки прихватљивим, при чему је експериментални наноструктурни ALBO-CA показао нешто бољи ткивни одговор након поткожне имплантације код пацова.

Кључне ријечи: биокомпатибилност, наноструктурни калцијум-алуминат, DiaRoot Bioaggregat, поткожно везивно ткиво.

Paper received: 22 August 2023 **Paper accepted: 26 April 2024**