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The Comparative Effects of Platelet-Rich Plasma and Polycaprolactone-Hydroxyapatite Zeolite Nanocomposites on Wound Healing After Tooth Extraction

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Abstract

Objectives: Post tooth extraction type of wound healing is a convoluted process that helps wounds reform. This study aims to evaluate the impact of polycaprolactone-hydroxyapatite zeolite nanocomposites on the healing processes of mucosa overlying post-extraction alveolus.

Materials and Methods: Fifteen healthy cats with premolar lower tooth involvement were selected for tooth extraction. The biopsy sampling from the mucosa of the alveolus was performed on the 10th postoperative day. The cats were grouped as control, platelet-rich plasma (PRP), and nano polycaprolactone-hydroxyapatite zeolite.

Results: The histopathologic analysis showed that contrary to controls and PRP, the nano group had a lower presence of inflammatory cells, a complete irregular thick epithelium, more granulation tissue, and more fibrosis. So, nano polycaprolactone-hydroxyapatite zeolite accelerated the healing process after tooth extraction.

Conclusion: Nanocomposite containing nano zeolite can improve wound healing after tooth extraction.

Keywords: Nanocomposite, Polycaprolactone-hydroxyapatite-zeolite, Tooth extract, Cavity, Wound healing

Introduction

Gingivitis with severe pain may be accompanied by dental surgery. A dry socket is a painful dental located gingivitis and ulcer after tooth extraction. It happens due to failing to develop a good blood clot at the tooth extraction site before the wound has healed (1). The healing process is accompanied by coagulation, inflammation, and fibrosis. The platelets release matrix components, growth factors, and chemokines in the clotting phase. The second phase starts with synchronous cellular chemotaxis and migration to remove debris. The granulation tissue is the third phase, facilitating the blood supply, and at the end phase, collagen is deposited and organized (2).

Molar teeth extraction is often associated with ulcers and massive inflammation (3). Oxidative stress, C-reactive protein, fibrinogen, and leukocyte infiltration are the reasons for the local edema and pain in the first days after surgery (4). Routine wound healing may take a chronic process and need more care to resolve increased tissue destruction, necrosis, and pain (5).

Clinicians administrate glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) to suppress edema and inflammatory cells. These powerful anti-inflammatory drugs may promote gastritis and local infection (6). The discovery of novel options that accelerate wound healing, significantly reducing the use of drugs, has been a priority in the last years and improved the evolution and application of scaffold therapy (7).

Platelet-derived products have gained popularity as a novel option, mainly due to their high concentrations of bioactive molecules such as growth factors and cytokines, which play important roles in tissue healing and regeneration. In a study, the use of platelet-rich plasma (PRP) significantly accelerated tissue healing and regeneration process and facilitated nerve regeneration process on peri-implant innervation in dog mandibles (8). The addition of PRP enhances bone formation after three months and may be clinically effective in accelerating postsurgical healing in both periodontal and maxillofacial surgical applications in dogs (9). A pilot study showed that the treatment of critical-sized defects of the mandibles of dogs with polycaprolactone-20% tricalcium phosphate (PCL-TCP) scaffolds may be augmented by the addition of PRP (10). The PRP and hydroxyapatite (HA) exploit low mechanical stimulation to favor granulation tissue and then after bone tissue formation (11,12). Ag nanocomposites zeolite/TiO2 in dentistry and medicine demonstrated antibacterial, anti-inflammatory, and regenerative activity (13). Elastic therapeutic tape effectively decreased trismus and swelling after extraction of molar teeth (14). Zeolite

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Key Messages

- In today's world, the wound after tooth extraction can be very painful or slow to heal, and it may become a severe problem. This study presented better-wound healing using a zeolite nanocomposite scaffold.

nano component provides a practical approach for accelerating infected wound healing through bactericidal ability and modulating inflammation. It may be developed for the treatment of various bacterial infections (15). PCL is a polymer in fabricating scaffolds for wound healing (16). Some studies mixed the PCL and HA to produce bio-scaffolds used in bone regeneration (17). A study confirmed that nano-hydroxyapatite with polydopamine could improve the healing of infected wounds. This happens through its ability to kill bacteria, granulate tissue formation, modulate inflammation, more collagen synthesis, and angiogenesis (18). Accordingly, this study aimed to develop a scaffold for a broad spectrum of wound healing and gingiva reconstruction.

Material and Methods

Study Design and Animals

This prospective randomized veterinary clinical trial study was conducted in a private clinic. Inclusion criteria were the necessity to extract mandibular premolars, and the presence of premolars in the same anatomical conditions. The exclusion criteria were pregnancy, lactation, chronic infections, and the reported diagnosis of liver, renal, and cardiovascular diseases. The sample size included surgery of five teeth in each group to achieve a statistical significance (alpha value = 0.05). Fifteen client-owned adult domesticated short hair cats (5-8.5 years old) with premolar teeth carries were selected from the university clinic between September 2021 and May 2022. All cats were subjected to antibiotic therapy initiated from the day before surgery for six days. The animals were divided into three groups: Control: without any treatment after suturing the alveolar defect; PRP: injection of PRP in the alveolar defect before suturing; and nano: injection of nano HA particles with zeolite in the alveolar defect before suturing.

Preparing Nano Composites

To prepare nano composites, we dissolved 0.8 g of PCL in 20 mL of solvent (1, 4-dioxane) for 6 hours at 60°C with stirring. Then, 0.0025 g of HA was solved in 5 mL of solvent. After that, it was sonicated for 10 minutes to provide the 0.05% HA nanoparticles. Next, we prepared 10% zeolite nanoparticles in the form of 0.5 g of zeolite in 5 mL of solvent dispersion and sonicated and stirred it for 10 minutes in a row. The three prepared solutions were mixed and stirred continuously for 1 hour. Then, it was immediately transferred to a freezer at -70°C.

EDAX TEAM software manual revealed that the HA and zeolite nanoparticles were homogeneously dispersed inside nanoporous PCL. Estimating the elemental composition of zeolite (aluminosilicate) and HA showed the compounds with defined proportions. Also, the morphology of the nanocomposite was utterly determined (Figure 1).

In the Fourier-transform infrared spectroscopy (FTIR), the most significant peak was the carbonyl ε-Caprolactone vibration bond seen in the 1730 region. About 2900 to 2950 peaks were related to the tensile bond of hydrogen carbon of methyl and methylene groups (CH2, CH3). P-O tensile vibrations were visible in the range of 1068 and 960. Other peaks related to the polymer structure in 1088 to 1110 were related to the vibration bond of carbon-carbon, carbon-oxygen, and carbon-oxygen-carbon. Tensile vibrations were related to the OH bond of the internal groups Al-O-H in region 736. The two vibrations in regions 1532 and 1463 belonged to the Si-O-Si and Al-O-Si bond vibrations of the zeolite, respectively (Table 1, Figure 2).

Preparing PRP

To prepare PRP, 16 mL of blood was taken from a jugular

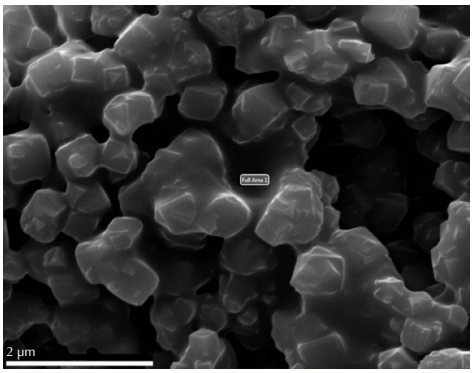

Figure 1. The SEM Images of Polycaprolactone/Hydroxyapatite-Zeolite Nanocomposite. Hydroxyapatite-zeolite nanoparticles were homogeneously dispersed inside nanoporous polycaprolactone (Scale: 2 µm. Magnification: 20000×).

Table 1. FTIR spectra of the polycaprolactone/hydroxyapatite-zeolite nanocomposite

Peak Number	X (cm-1)	Y (%T)
1	2954.30	92.59
2	1730.17	71.66
3	1598.62	96.84
4	1532.93	95.85
5	1463.68	95.09
6	1400.25	94.70
7	1370.50	93.22
8	1263.97	87.36
9	1221.92	91.41
10	1175.53	82.25
11	1068.21	93.22
12	960.45	94.63
13	736.49	97.02

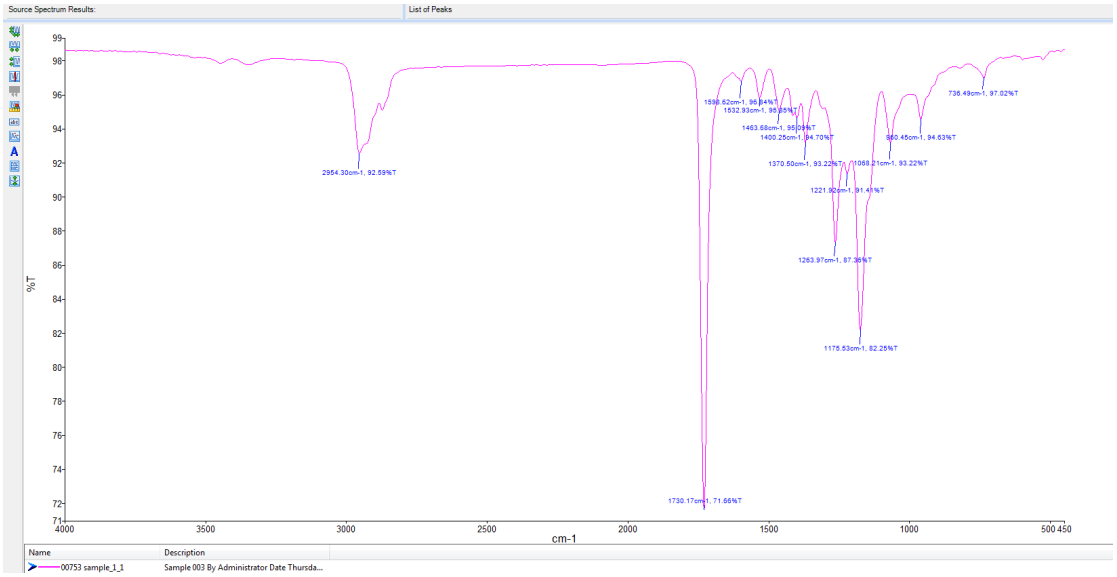

Figure 2. FTIR Spectra of the Polycaprolactone/Hydroxyapatite-Zeolite Nanocomposite. In the FTIR, the most significant peak was the carbonyl caprolactone vibration bond seen in the 1730 region. About 2900 to 2950 peaks were related to the tensile bond of hydrogen carbon of methyl and methylene groups (CH2, CH3). P-O tensile vibrations were visible in the range of 1068 and 960. Other peaks related to the polymer structure in 1088 to 1110 were related to the vibration bond of carbon-carbon, carbon-oxygen, and carbon-oxygen-carbon.

vein and poured into two heparin vacutainers. Blood was centrifuged for 20 minutes at 2800 pm. In this way, the blood was divided into three separate parts: red blood cell, PRP, and plasma-poor platelet (PPP). The part containing platelets and mononuclear cells was finely separated by a spinal needle and mixed with the remaining 2 mL of plasma. The final solution was placed in a sterile vacutainer and centrifuged at 1300 RPM for 15 minutes. After that, PPP remained at the top of the vacutainer, and PRP remained at the bottom. The final PRP was obtained by separating the PPP from the vacutainer.

Preparing to Surgery

The first visit included a clinical and radiographic examination which confirmed the necessity of bilateral extraction of impacted lower premolars. All cats received diazepam (0.22 mg/kg Zepadic®; Caspian Tamin Pharmaceutical Co., Rasht, Iran) and ketamine (10 mg/kg Ketalar®; Alfasan) combination (19). The mouths were rinsed before the extraction with 0.2% chlorhexidine gluconate. The practical surgeon with standardized technique operation on all cats was the same. The trained surgeon operated a standardized surgical technique on all cats, and one tooth of each cat was removed.

The Surgical Procedure

First, a trapezoidal flap was developed using an incision from the lower premolar base at about 3 mm from the gingival sulcus. Dental Luxator entered the periodontal space and tried to loosen the periodontal ligament. After ensuring that it was loose enough, the tooth was extracted using a dental extractor. Bleeding was controlled by applying pressure to the site, and the mouth was rinsed again with chlorhexidine. The cavity was filled with homogeneous PRP liquid and nano hydroxyl apatite-PCL before suturing in the PRP and nano particles of nano groups. Vicryl 0-4 suture was used as a simple interrupted suture pattern.

Histopathological Evaluation

Ten days post-surgery, a biopsy was performed from the site of surgery. After fixation in the 10% formalin and tissue processing, the histopathological evaluation was followed according to scoring system clarified in Table 2.

Statistical Analysis

Numerical data were demonstrated as SD means and evaluated by GraphPad Prism 9. The Kolmogorov-Smirnov test evaluated the normality of distribution. The Wilcoxon signed-rank test was performed to compare the means of each group's variables. The one-way analysis of variance (ANOVA) followed by the Tukey's post hoc test was used for the multiple comparisons means. The significance level was P <0.05.

Results

Ten days after surgery, the socket of extraction in all groups did not show any necrosis, hemorrhage, and pus discharge except mild signs of edema.

Inflammation

Numerous inflammatory cells were spread in the granulation tissue underlying the basement membrane of the control and PRP groups. Exocytosis of numerous lymphocytes was adjacent to the epidermis. The infiltration rate was at least in the nano group (Figures 3, 4).

Table 2. Histopathological Scoring of the Healing Tissue From Teeth Extracted Alveolar Defect in the Cats

Healing parameters	Findings	Score Number
Inflammation	Inside the clot and perivasculitis involved more than half in the high-power field	1
	Inside the clot and perivasculitis involved 1/2 to 1/4 in the high-power field	2
	Inside the clot and perivasculitis involved less than 1/4 in the high-power field	3
	Inside the clot and perivasculitis and connective tissue	4
	Inside the clot and perivasculitis only	5
	Inside the clot only	6
	Around the margin	7
	No inflammation	8
Fibroplasia	No granulation tissue	1
	Primary granulation tissue	2
	High cellular granulation tissue	3
	Primary collagen precipitate in the granulation tissue	4
	Bundles of collagen in the granulation tissue	5
	Regular more bundles of collagen in the granulation tissue	6
Fibrosis	No collagen	1
	Newly finely collagen in the granulation tissue	2
	Lamina propria fibrosis	3
	Dermal fibrosis	4
	Deep tissues fibrosis	5
Epithelialization	No regeneration	1
	Start regeneration	2
	Epithelium cover up to half of the surface	3
	Epithelium cover more than half of the surface	4
	Complete irregular epithelium	5
	Normal epithelium	6

Fibroplasia

Unlike the nano group, the amount of granulation tissue formation and collagen production in the Control and PRP groups had little development, indicating a significant difference between them. The nano group had more collagen bundles, showing significant differences with PRP and the Control (Figures 3 and 4).

Fibrosis

The rate of fibrotic tissue formation and the regularity of collagen bundles in the Control and PRP groups were less developed than in the Nano group, indicating a significant difference between them . Also, the nano group had more fibroblasts and regular collagen bundles with a significant difference (Figures 3 and 4).

Epithelialization

The amount of epithelial tissue formation in the control group, like the PRP group, did not cover the wound surface, but there was no significant difference. In contrast, the Nano group had a complete epithelium with a significant difference (Figures 3 and 4).

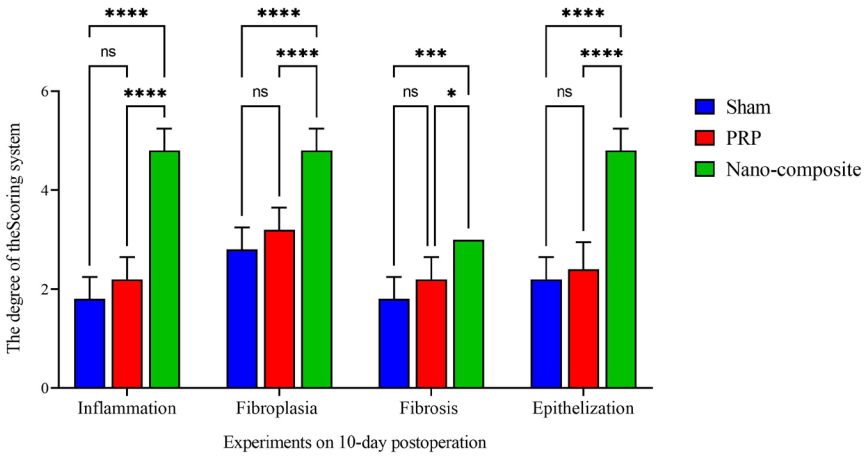

Figure 3. Histopathological Scoring of the Tissue Around the Alveolar Cavity.

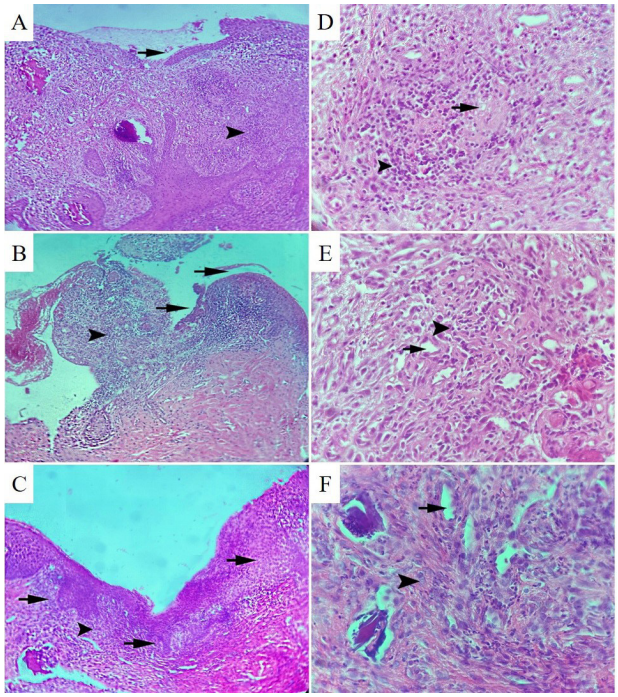

Figure 4. Tissue Cross-section Around the Alveolar Cavity. A, B, C: The epithelial tissue migration (arrow) was well developed only in the Nano group. The numerous inflammatory cells (arrowhead) were seen more in the Control and PRP groups. The fibroplasia and fibrosis were as of that in the epithelial score. D, E, F: Higher magnification field of the sections revealed more new blood vessels (arrow) in the granulation tissue of the Nano group compared to the Control, but there was more leukocyte infiltration in the Control and PRP groups (H&E, A, B, C: ×10; D, E, F: ×40).

Discussion

Generally, the wound healing process consists of the phase of inflammation of about three days, the proliferative phase from the third day to the 14th day, and the remodeling phase that endures months but, in some cases, endures years. In the oral cavity, various types of wounds are constantly subjected to the effects of bacteria, food waste, and saliva that could interrupt the healing process (20). Periodontal diseases are among the most common oral diseases in dogs and cats. Most teeth that suffer from tooth decay are premolars 3 and 4 and molar (21). Because dental care in domestic animals is indigent, the disease progresses a lot when it comes to the clinic and leads to tooth extraction. Therefore, 3 and 4 mandibular premolars with advanced periodontal disease stages were used in this study. Both open and closed techniques can extract multi-rooted teeth such as premolars. The closed method was used in some studies (22,23). Covering the surface of the remaining tooth cavity and filling the alveolar socket have been recommended to prevent the dry socket formation (21). However, no clinical studies have been performed in this regard.

In this study, the PCL-HA zeolite nanocomposite was named as Nano group. We aimed to prove whether nanocomposite could improve overlying tooth extraction mucosa better than PRP. The location of the extracted tooth is like an open wound in which the alveolar bone is also exposed. If the tooth extracted cavity is left open for the gradual formation of granulation tissue, water-soluble food debris will penetrate the cavity, and there will be a place to absorb the infection (22). The open cavity causes more pain and risks of malformation, slowness, and infection. Suturing the cavity after tooth extraction accelerates wound healing, but gingival tissue does not have enough flexible space to support suturing. Stretching the wound surface is a risk of improper repair or damage due to further rupture (24). Another disadvantage of sutures is the need for incisions to release more gum tissue, reducing blood flow to the wound edge. Recently, cavities have been filled with various biological or synthetic materials to prevent the filling of the extracted tooth and prevent the formation of dry sockets. A dry socket is a common and painful problem after tooth extraction. Researchers have always tried to devise a suitable method to prevent its occurrence (25). HA could protect the socket against various harmful penetrating debris and microbes. The histomorphometric evaluation of HA effects demonstrated less debris of graft materials. Bridging protection could care for every extraction cavities to retain the healthy bone for successful restoration (26). The PRP application in the tooth extraction cavity could improve soft and hard tissue healing. Various ranges of mesenchymal and epithelial cells, such as fibroblasts and keratinocytes, in cooperation with macrophages, are targets of the PRP for improving the wound healing process (27). A study revealed that use of biomaterials with PRP in post-extraction sites of the mandibular tooth in dogs can make the repair process more efficient and accelerate the healing process (8). A recent study revealed that PRP could reduce post-dental extraction pain and inflammation on the first day to ten days after tooth extraction. However, PRP's actual mechanisms of action have not been completely comprehended, and there is still controversy about the actual usefulness of this treatment (28). In this study, we could not show the improving effects of PRP on the healing process more than the Control group, which is inconsistent with some other reports. A study reported that a 20% weight/volume PCL scaffold could cover the dental cavity and facilitate cell proliferation and growth as biohybrid implants (29). Also, some studies suggested that combined PCL/HA scaffolds accelerate the regeneration of bone defects. We tried to create a better process than PRP by preparing a mixture of all items in the nanocomposite. The results were as expected in terms of the therapist's effects. Each component of this nanocomposite had been worked on in previous studies and was influential in healing the wound healing process. The sum of these composites we prepared in nano-size also showed satisfactory improving effects. However, we witnessed the opposite effects in the PRP group and did not see much effect compared to the Control group. In the Nano group, all factors, including reduction of inflammation, fibroplasia, fibrosis,

and epithelium formation, showed a favorable trend. The healing process after tooth extraction had the best histological characteristics in the nanocomposite group. This result means improved wound healing.

Authors' Contribution

Conceptualization: Alireza Jahandideh.
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Formal Analysis: Pejman Mortazavi.
Investigation: Alireza Sagart.
Resources: Ahmad Asghari, Abolfazlb Akbarzadeh.
Data Curation: Alireza Sagart.
Writing—Original Draft Preparation: Alireza Sagart.
Writing—Review and Editing: Alireza Sagart, Alireza Jahandideh.
Visualization: Alireza Sagart.
Supervision: Alireza Jahandideh.
Project Administration: Abolfazlb Akbarzadeh.
Funding Acquisition: Alireza Sagart.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

This article has been conducted on animals under the rules of the university's ethics committee.

Financial Support

None.

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