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Research Article

Effect of β-tri-calcium phosphate in both its putty and granular forms in treating bone defects in sheep

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Abstract: The present study aims to evaluate and compare the effect of β-tri-calcium phosphate granules and Putty on the healing of bony defects after induced injury on the tibia bone of sheep. **Materials and Methods:** Four healthy local breed male sheep all the sheep from the same farm. Four intervals were performed (2 weeks, 4 weeks, 6 weeks, 8 weeks). One tibia in each sheep was operated on at two two-week interval periods between each surgery (one surgery on each sheep making a total observation period of eight weeks). After two weeks of the last operation, the animals were euthanized based on a scheduled timeline. **Results:** The study reveals significant changes in osteoblasts, osteocytes, new capillaries, and histomorphometric measurements of bone marrow space over time ,The study presents histological sections of sheep treated with granules and putty, revealing changes in bone marrow space histomorphometry and the presence of bone cells and capillaries. **Conclusion:** Although both kinds of β-TCP putty and granules considerably improved bone fracture healing, the β-TCP putty demonstrated a better and faster healing ability than the granules, with a marked improvement in the bone marrow area.

Keywords: Bone marrow space, Granules β-TCP, Putty β-TCP

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INTRODUCTION

Malignant tumors and severe trauma can cause massive bone defects, requiring various treatments like induced membrane technique, allogenic bone grafting, synthetic bone grafting, artificial joint replacement, and autologous bone grafting [1].

Bone grafting is a common dental procedure used in dental implants, ridge augmentation, sinus lift, socket preservation, and periodontal therapy [2]. Bone tissue's regeneration capability allows for easy healing of defects or fractures, but in severe cases, these pathways are obstructed [3]. Alloplastic graft materials, including calcium sulfate, tri-calcium phosphate, and coralline hydroxyapatite, are synthetic grafting materials with osteoconductive properties [4]. The development of injectable materials like putties, cements, and gels has sparked interest in bone regeneration due to their adaptability to bone defect morphology [5]. Injectable dental putties in syringes are a next-generation Beta Tri-calcium-phosphosilicate bone graft material with enhanced handling characteristics. It's made from bioactive glass with additives like HPMC and glycerin, and absorbed during implantation for tissue infiltration [6].

Putty received FDA and CE approval for dental indications in 2007. It was the first synthetic putty that didn't need to be handled or manipulated, and it was also the first to come in a greatly simpler cartridge delivery system. The use of calcium phosphosilicate putty minimizes graft waste and chair-side time. Unlike previous bioinert synthetic grafts, CPS putty is a bioactive regenerative material that not only works as an osteoconductive scaffold but also interacts with surrounding tissues and provides osteostimulatory effects [6]. The aim is to evaluate and compare the effect of **β-tri-calcium phosphate Putty** and Granules on the healing of bony defects after induced on sheep.

MATERIALS AND METHODS

Chemicals and medicine

Beta-tri calcium phosphate (β-TCP) Putty and Granule from powerbone® is an injectable and formable putty bone graft based on hydrogel Beta-tri calcium phosphate (β-TCP) granules or powder, including ZrO_2 particles for antibacterial efficacy.

Animals

Four healthy local breed male sheep (age 1-1.5 years), numbered 1-4, weighting (40-50kg) (range 45kg) enrolled in the study, all the sheep from the same farm. Veterinarian regularly supervised their health and feeding. Animals were acclimated for two weeks before any procedure and general state inspected to ensure the absence of general or infectious disease. To avoid operator-mediated errors, all surgeries were performed by the same surgeon and at a stable temperature Figure 1.

Figure (1): Three holes of bone defects with treatment (groups of study)

Study design

Four healthy local breed male sheep (age 1-1.5 years), numbered from 1-4, weighting (40-50kg) (range 45kg) was used in the study. Four intervals were performed (2 weeks, 4 weeks, 6 weeks,8 weeks). One tibia of each sheep was operated on, with an interval of two weeks between each operation, so that each sheep gave me four observation periods. After two weeks of the last operation, the animals were euthanized based on a scheduled timeline. The groups were:

- **Group1 (2 weeks):** three defects on each tibia β-tri-calcium phosphate granules, control negative, β-tri-calcium phospha Putty.
- **Group2 (4 weeks):** three defects on each tibia β-tricalcium phosphate granules, control negative, β-tri-calcium phospha Putty
- **Group3 (6 weeks):** three defects on each tibia β-tricalcium phosphate granules, control negative, β-tri-calcium phospha Putty
- **Group4 (8 weeks):** three defects on each tibia β-tri-calcium phosphate Granule, Control negative, β-tri-calcium phosphate Putty

Statistical analysis

A computer package (Sigma Stat V12.0 / SYSTAT software) was used to conduct the histomorphometric analysis. Data were presented as means ± SE (standard error) and were analyzed by One Way ANOVA test using Duncan's test with a significant level set on P<0.05. The non-parametric data of Ki67 immunohistochemical scores were analyzed as median and IQR(Inter-Quartile-Range) by Kruskal-Walli's test using Tukey Test with a significant level set on *P*<0.05.

RESULTS

Histological study

This study examined sheep tibial bone histological sections to analyze the effects of treatments and periods on bone histomorphometry, revealing osteoblasts, osteocytes, and new capillaries. The study reveals significant changes in osteoblasts, osteocytes, new capillaries, and histomorphometric measurements of bone marrow space over time, highlighting the significant changes observed in control groups.

Figures 2 to 17 correspond to granules-treated groups at 2, 4, 6, and 8 weeks, in Figures for Histological section of tibial bone of sheep of the granules-treated group showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain and 10X.

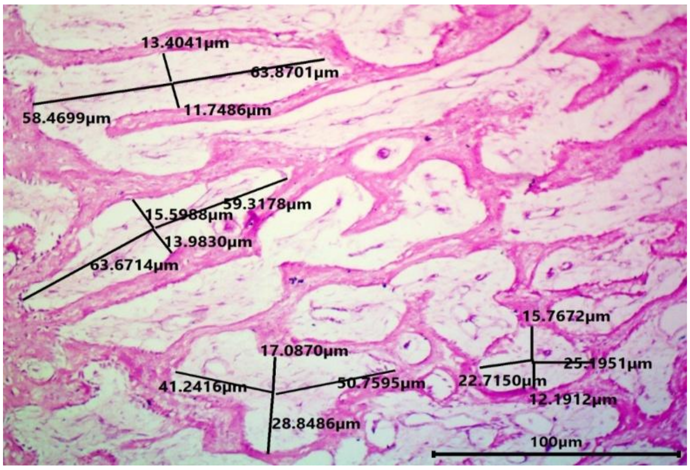

Figure (2): Histological section of tibial bone of sheep, **control negative (2 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

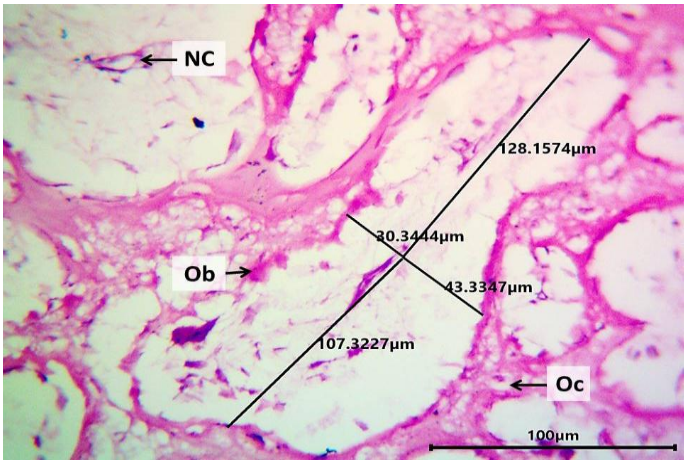

Figure (3): Histological section of tibial bone of sheep, **control negative (2 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc), new capillaries (NC), and the histomorphometric measurements of the bone marrow space. (994957 μm^2) space of field 40X. H&E stain.

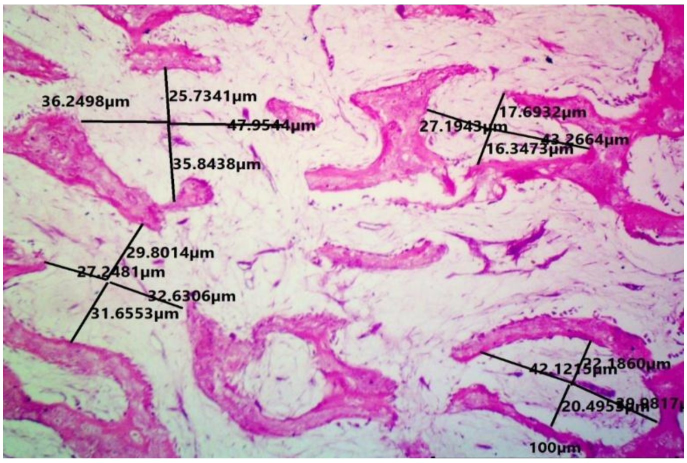

Figure (4): Histological section of tibial bone of sheep, **control negative (4 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

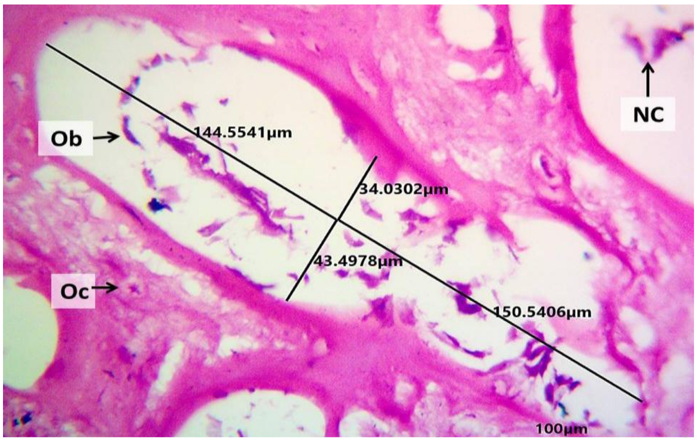

Figure (5): Histological section of tibial bone of sheep, **control negative (4 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc), and new capillaries (NC) and the histomorphometric measurements of the bone marrow space. 400X. H&E stain.

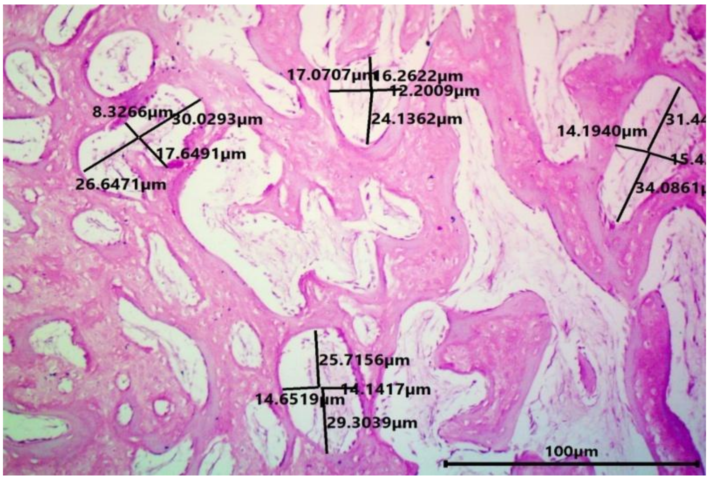

Figure (6): Histological section of tibial bone of sheep, **control negative (6 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

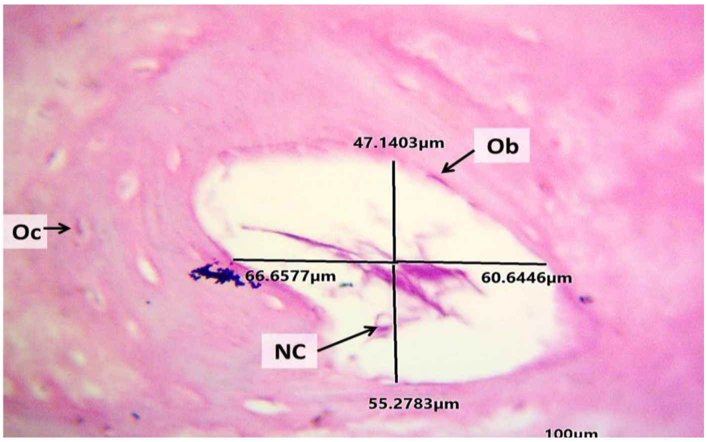

Figure (7): Histological section of tibial bone of sheep, **control negative (6 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

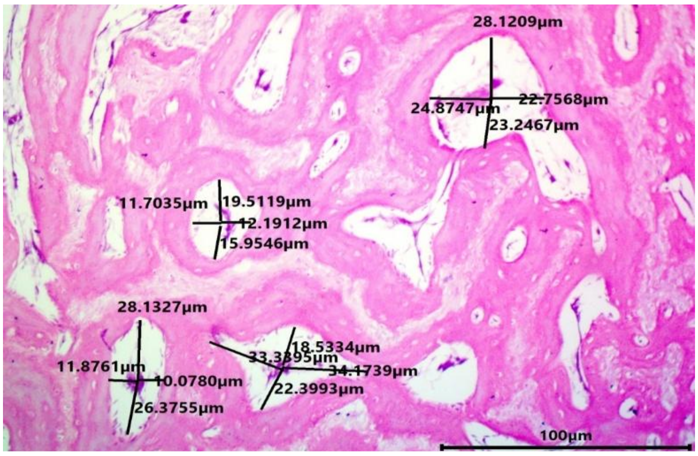

Figure (8): Histological section of tibial bone of sheep, **control negative (8 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

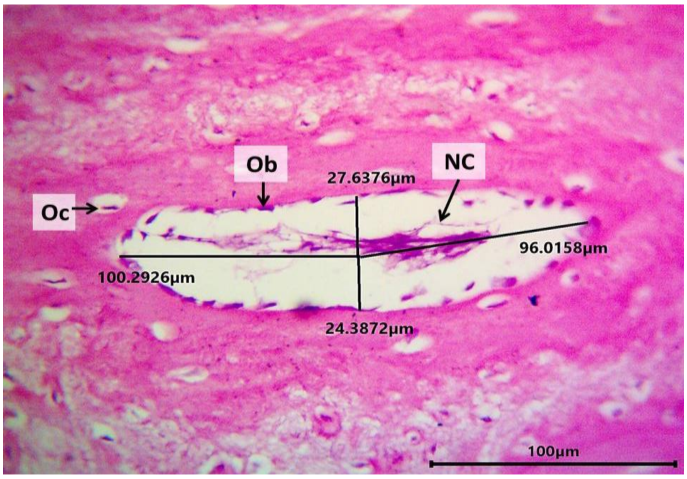

Figure (9): Histological section of tibial bone of sheep, **control negative (8 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

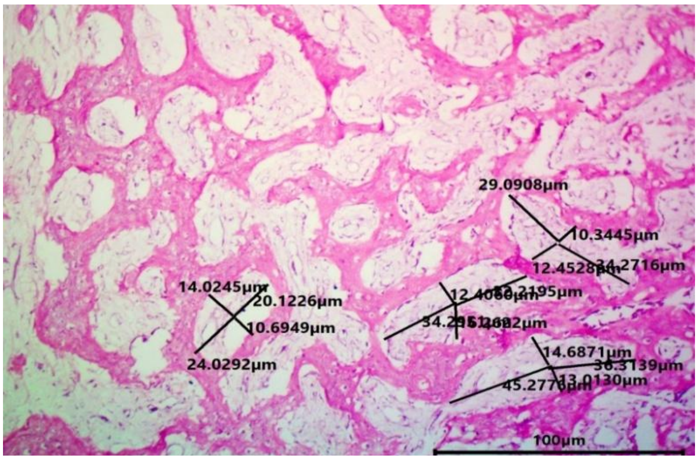

Figure (10): Histological section of tibial bone of sheep **of the powder treated (2 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

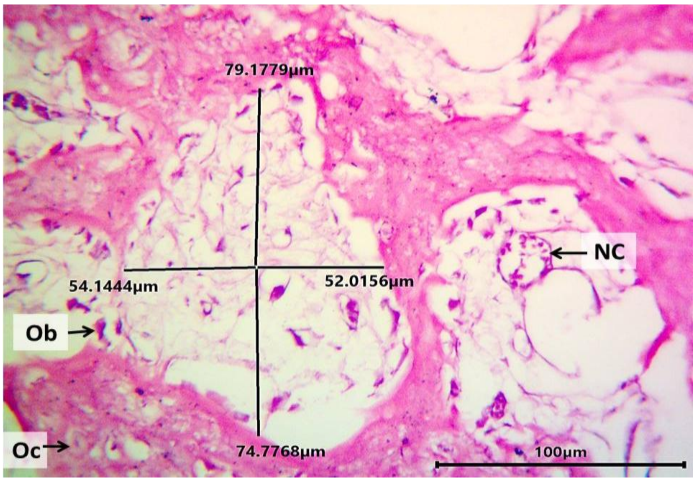

Figure (11): Histological section of tibial bone of sheep **of the powder treated (2 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X.

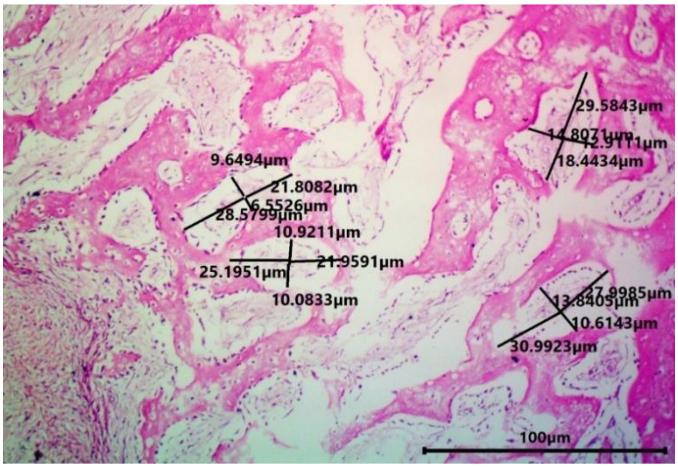

Figure (12): Histological section of tibial bone of sheep **of the powder treated (4 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

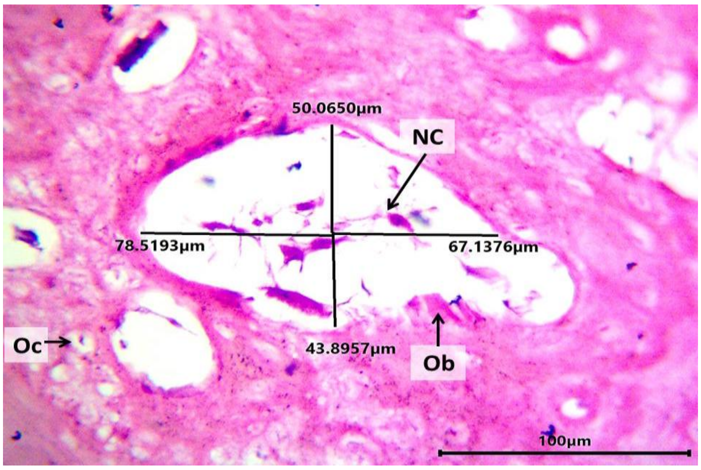

Figure (13): Histological section of tibial bone of sheep **of the powder treated (4 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X.

Figure (14): Histological section of tibial bone of sheep **of the powder treated (6 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

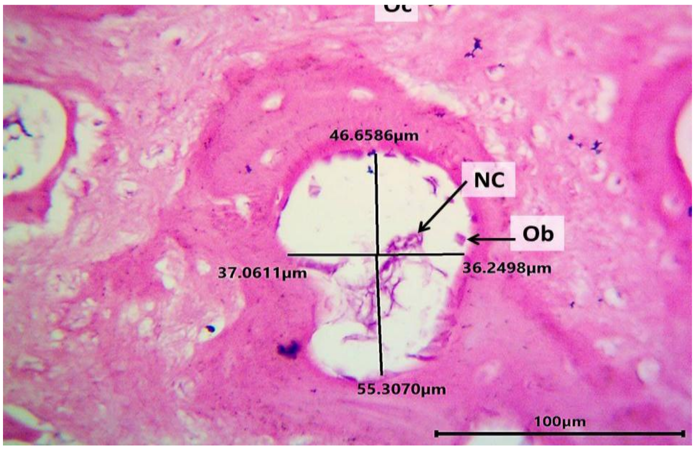

Figure (15): Histological section of tibial bone of sheep **of the powder treated (6 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

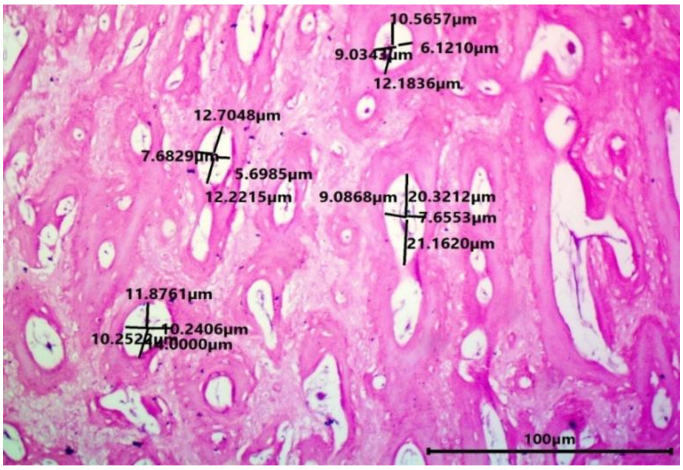

Figure (16): Histological section of tibial bone of sheep **of the powder treated (8 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

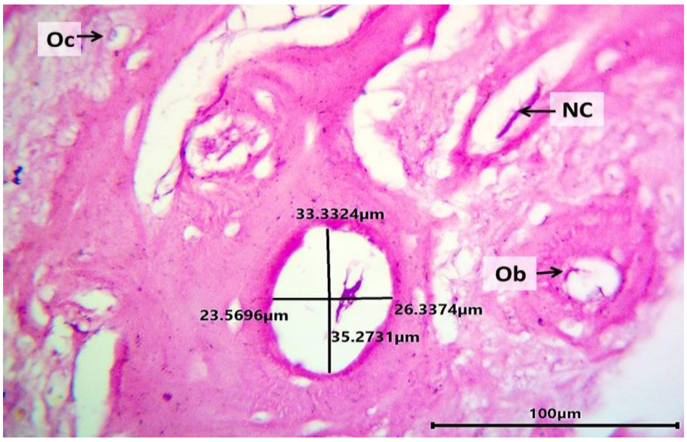

Figure (17): Histological section of tibial bone of sheep **of the powder treated (8 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

Figures 18 to 25 represent putty-treated groups within the same periods, displaying the variations in bone marrow space histomorphometry and the presence of bone cells and capillaries as significant components. showing the osteoblasts (Ob), osteocytes (Oc), and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X and 10X. H&E stain. These visualizations offer valuable insights into the dynamic changes within the tibial bone microenvironment under different treatments and time durations.

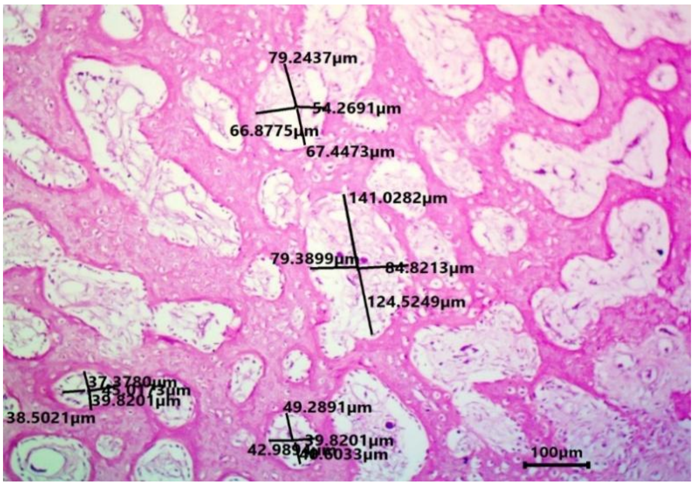

Figure (18): Histological section of tibial bone of the sheep **of the putty treated (2 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E

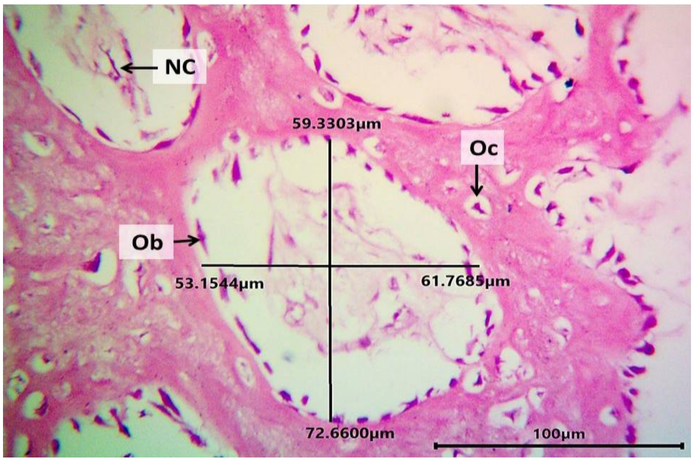

Figure (19): Histological section of tibial bone of the sheep **of the putty treated (2 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

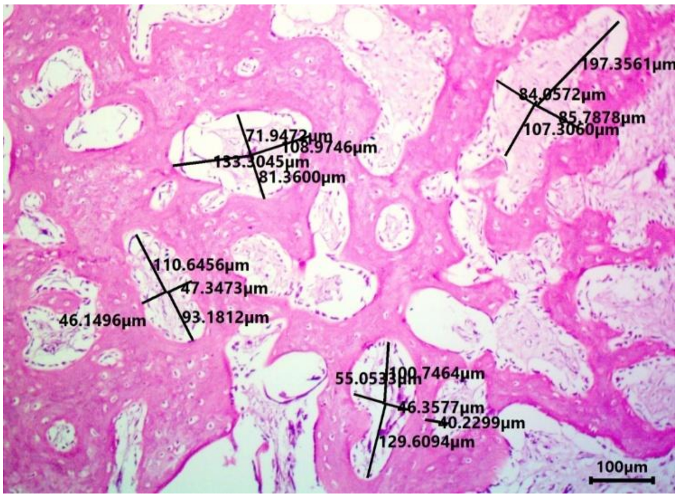

Figure (20): Histological section of tibial bone of the sheep **of the putty treated (4 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

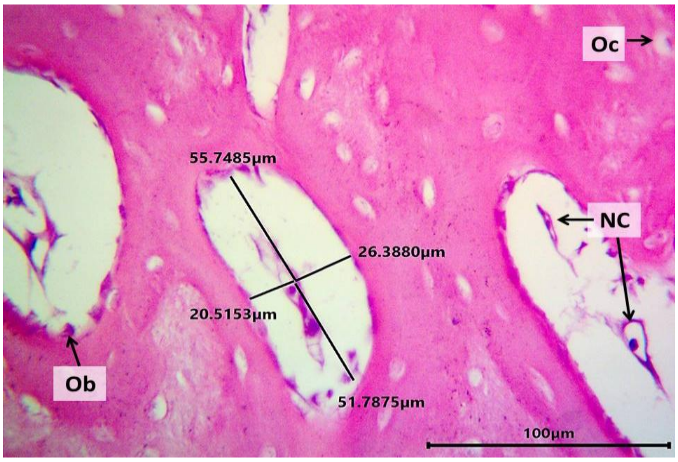

Figure (21): Histological section of tibial bone of the sheep **of the putty treated (4 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

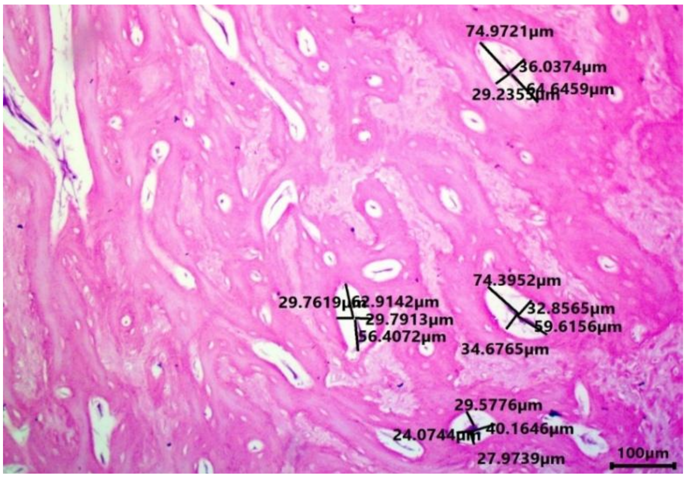

Figure (22): Histological section of tibial bone of the sheep **of the putty treated (6 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

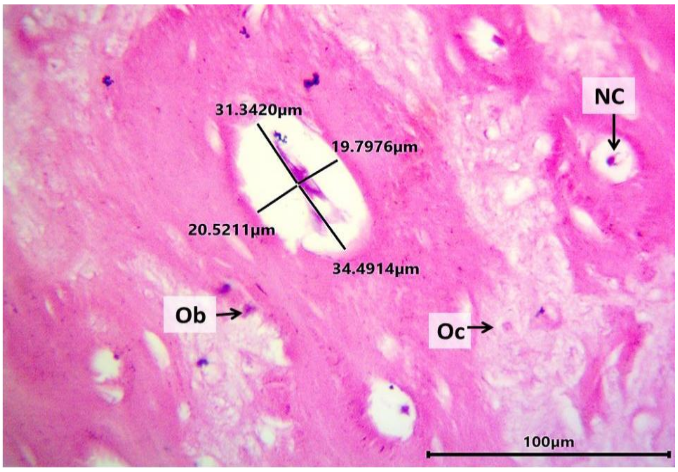

Figure (23): Histological section of tibial bone of the sheep **of the putty treated (6 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc) and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

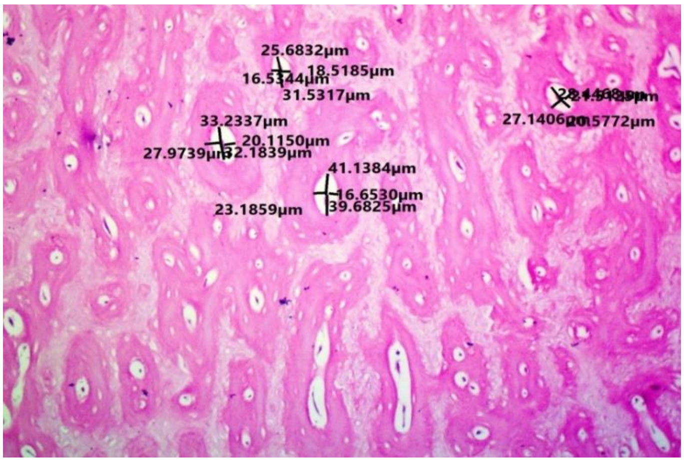

Figure (24): Histological section of tibial bone of the sheep **of the putty treated (8 weeks) group** showing the histomorphometric measurements of the bone marrow space. 10X. H&E stain.

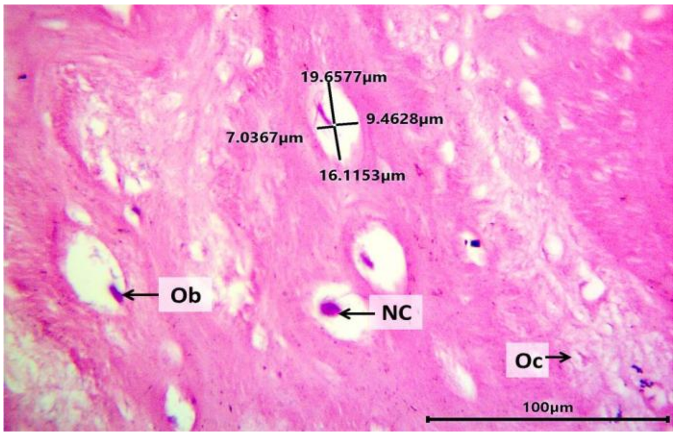

Figure (25): Histological section of tibial bone of the sheep **of the putty-treated (8 weeks) group** showing the osteoblasts (Ob), osteocytes (Oc), and new capillaries (NC), and the histomorphometric measurements of the bone marrow space. 40X. H&E stain.

Table (1) and Figure 26 show significant differences in bone marrow space measurements among three groups and four time periods. The type of material and time significantly affect bone marrow space. The putty and Granules group showed different bone marrow space values at 2 weeks significantly different from the values at 4,6,8 weeks, but the powder was recorded as less effective at lowering bone marrow area.

Table (1): The histomorphometry measurements of the bone marrow space in all groups and periods

Bone marrow space Mean ± SE	Control	Granules	Putty	*p*-Value
2w	112.5±6.89 aA	86.2±4.11 bA	72.7±4.67 bA	0.002
4w	75.5±7.03 aB	63.2±3.7 aAB	58.7±4.49 bB	0.030
6w	72.5±6.21 aB	56.2±2.49 bB	50.2±6.81 bB	0.046
8w	61±4.41 aB	30.2±4.13 bC	25.2±3.09 bC	<0.001
***p*-Value**	<0.001	<0.001	<0.001	

Data expressed as Mean ± stander error (N= 4 animals)
different small letters among material groups in rows mean there is a significant difference at $p \leq 0.05$
different capital letters among periods in column groups mean there is a significant difference at $p \leq 0.05$

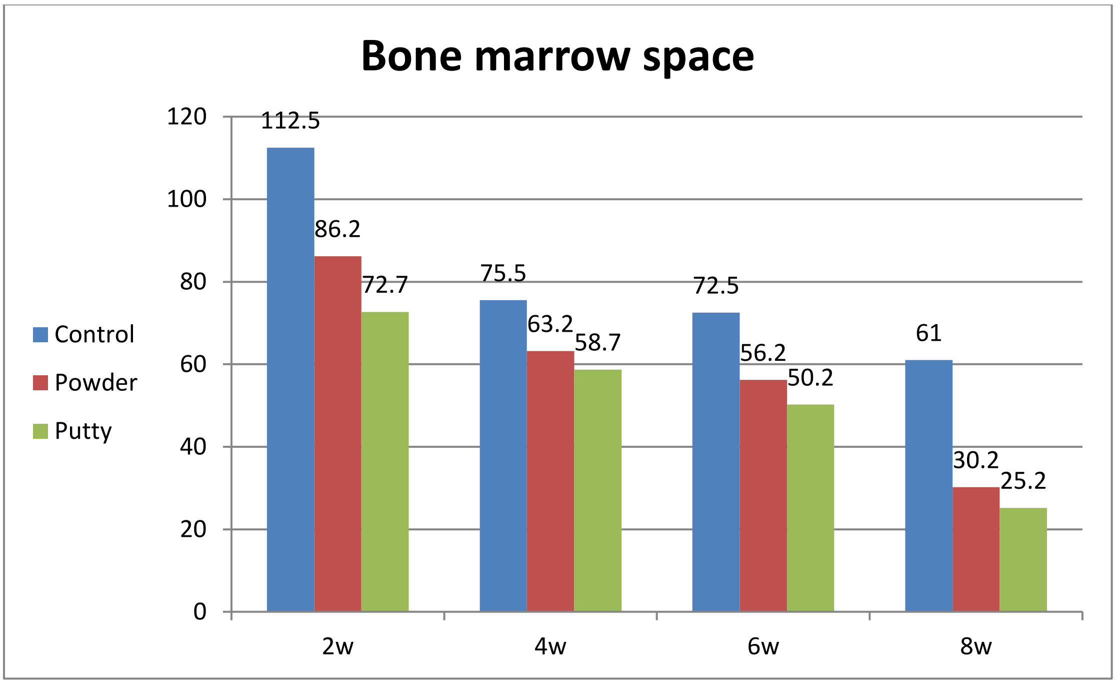

Figure (26): The histomorphometric measurements of the bone marrow space in all groups and periods

DISCUSSION

One of the basics of selecting animals for the experiment is knowing the purpose of the experiment, the extent of the animal model's similarity to humans, its availability, as well as the ease of dealing with it and its cost, these features make sheep an excellent model for experiments on bones [(7).] The current study found that using both putty and granules of β-TCP has a positive effect on repairing tibial bones in sheep, with minor differences in several histological findings. One of the reasons for these differences is that the β-TCP putty material has a higher viscosity than the granular material, making it easier to handle and apply to areas of bone injury, as well as the high porosity, which provides a surface with a large enough surface area for adhesion between bone cells and the rest of the components [8].

We discovered that the putty increases the quantity of bone trabeculae, bone marrow, and bone marrow area over time. This reflects the putty's effectiveness in treating bone fractures [9]. While β-TCP granules include fewer fluid substances and are more filling for shattered bone deformities, they also give support and take a longer time for results to manifest [10]. We discovered that, while β-TCP granules are successful at generating new bone trabeculae, it is less effective at lowering bone marrow area and bone defects when compared to the putty over the same time, which is consistent with bone [11] .

Histological changes:

After two weeks of treatment β-TCP granules: The findings revealed that there were early stages of healing, as evidenced by the presence of a rather big bone marrow area as well as some inflammation and swelling. We observed an uneven bone marrow area as a result of the presence of β-TCP granules, which take time to be absorbed and replaced by new bone [12].

After two weeks of treatment putty β-TCP: The presence of capillary blood vessels and new bone cells, which will be integrated into the new bone matrix after the gradual absorption of the β-TCP putty, is a good indicator of the beginning of the supply of oxygen and nutrients to the developing bone tissue [11].

The perimeter of the bone marrow area appears round, and the irregularity is practically identical to what was observed in the granule's treatment, which could be related to the rough surface of the putty, which takes time to absorb. Due to the large diameter of the bone marrow area, Figure 18 indicates the existence of an uneven circular mass in the center of the bone marrow, suggesting the putty substance used.

Individual variables, healing rate, particle size, and porosity all influence the length of β-TCP absorption [13].

After 4 weeks of treatment with granules β-TCP: The histological results appear to be more advanced in terms of the presence of a more circular bone marrow space that gradually fills with bone cells, and this depends on the extent of the granules resorption by the bone and its replacement with new tissue.

After 4 weeks of treatment with putty β-TCP: Figure 20 indicates a considerable decrease in the area and circumference of the bone marrow compared to Figure 18 and the two-week timeframe, where new capillary blood vessels and bony trabeculae appear to fill the gap and heal the defect. This demonstrates that the healing process is well underway. There are many molecules of material. β-TCP dispersed throughout the portions of the bone, indicating that the putty is still being absorbed by the bone.

After Six weeks of treatment with β-TCP putty: Overall, the histological findings in Figure 22 are consistent with the expected healing process for a bone defect treated with β-TCP putty at 6 weeks. The bone defect is almost filled in with new bone tissue and the β-TCP putty is much resorbed. The healing process is very close to completion (14).

After eight weeks of treatment with β-TCP granules: The histological appearance shows an almost complete completion of the healing process, with a reduced bone marrow area compared to a period of two and four weeks, as well as a decrease in the number of bone cells and the presence of blood vessels as healing approaches.

The decrease in bone marrow space area and perimeter is also likely due to the resorption of the β-TCP granules. As the bone defect heals, the β-TCP granules are replaced by new bone tissue. This process takes time, but it is essential for the complete healing of the bone defect (15).

After eight weeks of treatment with β-TCP putty: Figure 24 shows a very similar histological picture to Figure 18, which is of a bone defect treated with β-TCP putty at 2 weeks. The main difference is that there is much less β-TCP putty present in Figure 24. This indicates that the bone defect has healed significantly over the 6 weeks. Overall, the histological findings in Figure 24 suggest that the bone defect has healed very well .The histological findings in Figure 24 suggest that β-TCP putty is an effective material for promoting bone healing. At 8 weeks, the bone defect is completely filled in with new bone tissue, and the β-TCP putty is much resorbed. The healing process is very close to completion.

Faster Resorption, the histological findings indicate that the β-TCP putty is resorbed more quickly compared to the granules form. In the 8-week assessment, there is significantly less β-TCP putty remaining in the bone marrow space, suggesting a faster rate of resorption. This faster resorption is advantageous as it allows the bone to be replaced with new tissue more rapidly (16). Putty contains fewer intermolecular holes, a smaller surface area, and faster absorption than granules (Saska et al., 2015). As a result, the granules are frequently utilized in circumstances when additional support and time are required to heal broken bones (17).

Histomorphometric measurements

Based on the results, it appears that both Granules β-TCP and Putty β-TCP affect the bone marrow area. In comparison between Granules and putty β-TCP, at all periods, the area of bone marrow in both Granules -TCP and Putty -TCP is less than that in the control group. This suggests that -TCP is effective in reducing the size of bone marrow by influencing the microenvironment of the bone marrow, resulting in a reduction in the measured area (18; 19).

CONCLUSIONS

The results showed that both Granules β-TCP and Putty β-TCP have positive effects on the healing of bone fractures. Putty β-TCP showed a faster rate of resorption of the material and accelerated healing with an improvement in the forms of bone defects and a lesser inflammatory response. It was found that there was a decrease in the bone marrow space in both subjects compared to the control.

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Funding: This study is self-funded

Ethical statement: The study was conducted at the College of Veterinary / University of Mosul / Iraq, the study was conducted during 2021/2023.The approval from the Scientific Research Committee / Department of Oral and Maxillofacial Surgery / College of Dentistry / University of Mosul, (No. Uom. Dent.23/23).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript

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تأثير فوســفات ثلاثي الكالســيوم في كل من أشــكاله المعجون والحبيبية في علاج عيوب العظام في الأغنام

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الملخص

الاهداف: تهدف هذه الدراســة إلى تقييم ومقارنة تأثير حبيبات الفوســفات ثلاثي الكالســيوم والمعجون على شــفاء العيوب العظمية بعد الإصـابة المسـتحثة على عظم السـاق من الأغنام. **المواد وطرائق العمل**: أربع من سـلالة الأغنام الذكور المحلية جميع الأغنام من نفس المزرعة. تم تنفيذ أربع فترات (2 أسـابيع ، 4 أسـابيع ، 6 أسـابيع ، 8 أسـابيع). تم إجراء عملية جراحية لتحضـير واحد في كل خروف في فترتين فاصـلتين لمدة أسـبوعين بين كل عملية جراحية (عملية جراحية واحدة على كل خروف تجعل فترة المراقبة الإجمالية ثمانية أسـابيع). بعد أسـبوعين من العملية الأخيرة ، تم القتل الرحيم للحيوانات بناء على جدول زمني مجدول. **النتائج**: تكشـف الدراســة عن تغيرات كبيرة في بانيات العظم ، والخلايا العظمية ، والشـعيرات الدموية الجديدة ، والقياسـات النسـيجية لمسـاحة نخاع العظم بمرور الوقت ، وتعرض الدراسـة أقسـاما نسـيجية من الأغنام المعالجة بالحبيبات والمعجون ، وتكشـف عن تغيرات في قياس النسيج النسيجي لنخاع العظم ووجود خلايا العظام والشـعيرات الدموية. **الاسـتنتاجات**: على الرغم من أن كلا النوعين من-β تكب المعجون والحبيبات تحسن إلى حد كبير التئام كسر العظام ، أظهر المعجون-β تكب قدرة شفاء أفضل وأسرع من الحبيبات ، مع تحسن ملحوظ في منطقة نخاع العظام.