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ORIGINAL ARTICLE

Osteogenic effect of platelet-rich fibrin on a bone defect model of long bone in rabbits

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Severe defect of long bone is a major clinical concern in fracture patients with high-energy trauma. Successful fracture site union requires bone defect restoration, which could be achieved through various treatment options, including autogenic or allogenic bone grafts.[1-3] Autogenic bone grafts, typically harvested from the iliac bone, is known to exhibit superior osteogenic potential compared to allogenic grafts.[4] However, their clinical use may be limited by donor site morbidity and restricted amount availability.[5] Therefore, there remains a persistent need for alternative bone graft strategies that retain the superior osteogenic potential of autografts while avoiding donor site morbidity and limitations in graft availability.

Platelet-rich plasma (PRP) contains various growth factors, including platelet-derived growth

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ABSTRACT

Objectives: This study aims to evaluate the osteogenic effect of platelet-rich fibrin (PRF) graft with periosteal repair on a bone defect of long bone in rabbits, compared to control group that underwent periosteal repair alone.

Materials and methods: A total of 12 female New Zealand white rabbits were used in this study. Two rabbits were designated for PRP preparation, mixed with a human thrombin agent to produce PRF. A bone defect (5 mm in diameter and 7 mm in depth) was created in both proximal tibiae of 10 rabbits. The defect site of the right proximal tibia was filled with PRF, followed by periosteal repair (PRF group). In contrast, only periosteal repair was performed on the left proximal tibia (control group). For histological evaluation, hematoxylin and eosin (HE) and Masson's trichrome (MT) staining were performed at Weeks 4 and 8 after surgery. The bone healing ratio, defined as the proportion of newly formed bone area to surgically created defect area, was calculated to assess bone regeneration. For radiological examination, micro-computed tomography (micro-CT) was conducted at Week 8 after surgery.

Results: A total of nine rabbits survived until the planned euthanasia time points (four rabbits at Week 4 and five at Week 8). At Week 4 postoperatively, HE staining revealed a higher bone healing ratio in the PRF group compared to the control group; however, the difference was not statistically significant (PRF group: 71.0 ± 15.6, control group: 59.5 ± 18.1, $p = 0.34$). At Week 8 postoperatively, histological analysis showed no difference in the bone healing ratio between the two groups (PRF group: 79.3 ± 8.7, control group: 75.9 ± 13.2, $p = 0.55$). Micro-CT analysis demonstrated a superior Lane-Sandhu score in the PRF group compared to the control group, although this difference was not statistically significant ($p = 0.15$).

Conclusion: The PRF graft with periosteal repair appears to promote improved early-stage new bone formation in bone defects of long bone in an animal model compared to periosteal repair alone, although it does not reach statistical significance.

Keywords: Animal model, bone defect, long bone, platelet-rich fibrin, platelet-rich plasma, trauma.

factor, transforming growth factor beta-1, and vascular endothelial growth factor, which contribute to tendon and bone healing through multidirectional effects.[6,7] Despite its potential benefits, limited studies have explored the clinical application of PRP in bone defect treatment. This is primarily due to the fluid nature of PRP, which makes it challenging to retain at the bone defect site in clinical practice. To address this limitation, PRP can be fibrinized into platelet-rich fibrin (PRF), which is already used clinically for bone defects, particularly in dental surgery.[8] However, there are few studies in the literature to investigating the osteogenic effect of PRF on the bone defect of long bone in orthopedic surgery.

In the light of these data, in the present study, we hypothesized that the PRF graft with periosteal repair would result in superior new bone formation on a bone defect of long bone in rabbits, as assessed by histological and radiological examinations, compared to periosteal repair alone. We, therefore, aimed to evaluate the osteogenic effect of PRF grafting with periosteal repair on a bone defect of long bone in rabbits, compared to a control group that underwent periosteal repair alone.

MATERIALS AND METHODS

Study samples

All applicable international, national and institutional guidelines for the care and use of animals were followed. Experimental procedures were performed with approval from the Institutional Animal Care and Use Committee of the Clinical Research Institute (EWHA MEDIACUC 23-021). Twelve female New Zealand white rabbits, aged 12 weeks and weighing between 2,000 and 2,500 g, were used in this study. Five rabbits were scheduled for sacrifice at Week 4 after surgery for histological analysis, and another five at Week 8 for histological and radiological analysis. Two rabbits were designated for PRP preparation.

Preparation of PRP and fibrinization

A rabbit was anesthetized, and chest wall was sanitized. A total of 37 mL of blood was drawn via intracardiac puncture, and mixed with 3 mL of anticoagulant (Nothrom solution, AJU Pharmaceutical Corp., Korea). The anticoagulated blood was, then, processed using a commercial PRP preparation kit (Tricell, RevMed, Korea), which produces leukocyte-rich PRP through double-spin centrifugation (3,400 rpm for 5 min and 3,500 rpm for 4 min). Finally, 3 mL of PRP was collected and mixed with 4 mL of human thrombin (Evicel™, Johnson & Johnson Medical, USA) to obtain PRF (Figure 1). Using the same procedure, a total of two PRF preparations were obtained from each of the two rabbits. Each PRF preparation was used in the surgeries of five rabbits, resulting in a total of 10 rabbits receiving surgery.

Surgical procedure

A 3-cm longitudinal incision was made on the medial side of the proximal tibia. The subcutaneous fat layer and periosteum were dissected using a scalpel to expose the proximal tibial bone. A round bone defect, measuring 5 mm in diameter and 7 mm in depth, was created at the medial aspect of the proximal tibia perpendicular to the cortical bone using an awl. The bone defect site on the right proximal tibia was then filled with PRF, and the periosteum was repaired using simple vertical suture technique (PRF group) (Figure 2). In contrast, only periosteal repair using the same suture material was performed at the bone defect site on the left proximal tibia (control group).

Histological analysis

The rabbits were sacrificed at Weeks 4 or 8 post-surgery according to the block randomization method. Tissue samples from the bone defect sites of both proximal tibiae were collected from each rabbit, and fixed overnight in 10% neutral buffered formalin, and decalcified for five to six days in 4% hydrochloric acid. The samples were, then, embedded in paraffin using a Tissue Processor TP1020 (Leica, Biosystems, Nussloch

FIGURE 1. Representative image of the platelet-rich fibrin structure. The structural properties of platelet-rich fibrin make it a suitable grafting material for bone defect sites.

FIGURE 2. Platelet-rich fibrin grafting at the tibial bone defect site. **(a)** A round bone defect, measuring 5 mm in diameter and 7 mm in depth, was created at proximal tibia using an awl. **(b)** The defect site was filled with platelet-rich fibrin, followed by periosteal repair.

GmbH, Nussloch, Germany). The tissue sections were deparaffinized and rehydrated with xylene and decreasing alcohol concentrations. During sectioning, tissue sections were prepared perpendicular to the cortical bone to ensure that the cutting plane corresponded to the axis of the bone defect. Among the serial sections, the one that passed through the central region of the defect was selected for analysis. Sections 4-μm in thickness were stained with hematoxylin & eosin (HE) and Masson's trichrome (MT). The stained sections were examined under a microscope (BX51, Olympus, Tokyo, Japan), and digital images were captured using a slide scanner (Slideview VS200, Olympus, Tokyo, Japan). On the HE-stained images, the surgically defected bone area and the newly formed bone area were manually outlined and measured using the OlyVIA 3.4.1 (VS200-ASW) software (Olympus, Tokyo, Japan). The relative ratio (bone healing ratio) of the newly formed bone area to the surgically defected bone area was, then, calculated to evaluate the degree of bone regeneration.[9,10] On the MT-stained images, the healing quality of newly formed bone was scored from 0 to 4 according to the semi-quantitative histological scoring system.[11,12] All assessments were conducted by two experienced researchers, and the averages of two measurements were used in this study.

Radiological analysis

Before histological preparation of the eight-week specimens, micro-computed tomography (micro-CT) analysis was performed on the proximal tibial bone. After removing the residual soft tissue, the proximal tibia bone samples were fixed in a 1:1 solution of ethanol and sterile water for 24 h at room temperature. The specimen to be analyzed was positioned in the micro-CT scanner (SkyScan1173; Bruker-CT, Kontich, Belgium), ensuring that the center of the area to be measured was aligned. SkyScan1173 control software (Ver 1.6, Bruker-CT, Antwerp, Belgium) was used for the measurements. On the axial and sagittal images from the micro-CT scan, the quality of new bone formation was scored from 0 to 12 according to the Lane-Sandhu radiographic scoring system.[13,14]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The Mann-Whitney U test was used to analyze significant differences in the bone healing ratio, the semi-quantitative histological score and Lane-Sandhu score between the two groups. A p value of < 0.05 was considered statistically significant.

RESULTS

During the experimental period, one rabbit was excluded because of post-surgical death. Finally, nine rabbits (n = 9 tibiae in PRF group and

n = 9 in control group) survived until the planned euthanasia time points (four rabbits at Week 4 and five at Week 8).

At four weeks postoperatively, HE staining revealed a higher mean bone healing ratio in the PRF group compared to the control group, although the difference was not statistically significant (71.0 ± 15.6 in the PRF group, 59.5 ± 18.1 in the control group, $p = 0.34$) (Figure 3). However, at eight weeks postoperatively, no significant difference in the bone healing ratio was observed between the two groups (79.3 ± 8.7 in the PRF group, 75.9 ± 13.2 in the control group, $p = 0.55$). The MT staining showed that the PRF group exhibited more tightly organized new bone formation than the control group; however, there were no significant differences of the semi-quantitative histological scores between the two groups at Week 4 (2.8 ± 1.0 in the PRF group, 2.3 ± 0.5 in the control group, $p = 0.51$) and Week 8 (3.6 ± 0.5 in the PRF group, 3.0 ± 0.7 in the control group, $p = 0.20$) postoperatively (Figure 4).

Micro-CT analysis demonstrated a superior Lane-Sandhu radiographic score in the PRF group compared to the control group, although this difference also did not reach statistical significance (10 ± 1.9 in the PRF group, 8.2 ± 0.8 in the control group, $p = 0.15$) (Figure 5).

DISCUSSION

In the present study, we evaluated the osteogenic effect of PRF grafting with periosteal repair on a bone defect of long bone in rabbits, compared to a control group that underwent periosteal repair alone. The main finding of this study is that PRF grafting combined with periosteal repair tended to promote improved early-stage new bone formation with well-organized structure on a bone defect of long bone in rabbits, compared to periosteal repair alone, although there was no statistically significant difference. However, both approaches exhibited a similar degree of new bone formation at the final stage.

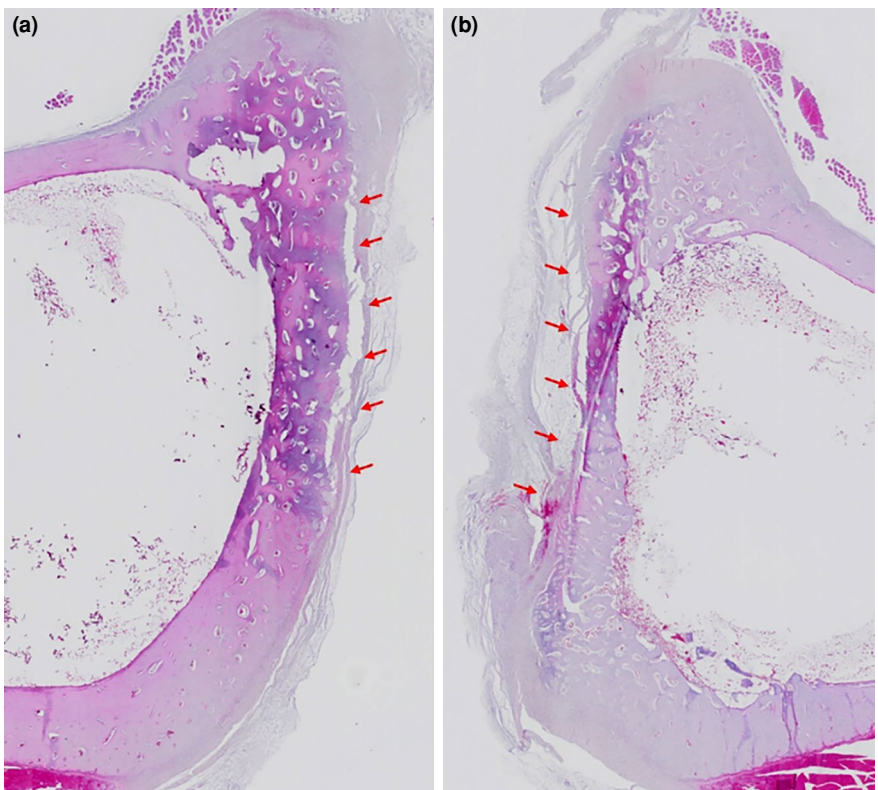

FIGURE 3. Hematoxylin and eosin staining at 4 Weeks post-surgery. The specimen that received PRF grafting with periosteal repair **(a)** exhibited the higher bone healing ratio than the specimen with only periosteal repair **(b)**. The red arrows indicate the bone defect area (H&E, ×20).
PRF, plasma-rich fibrin.

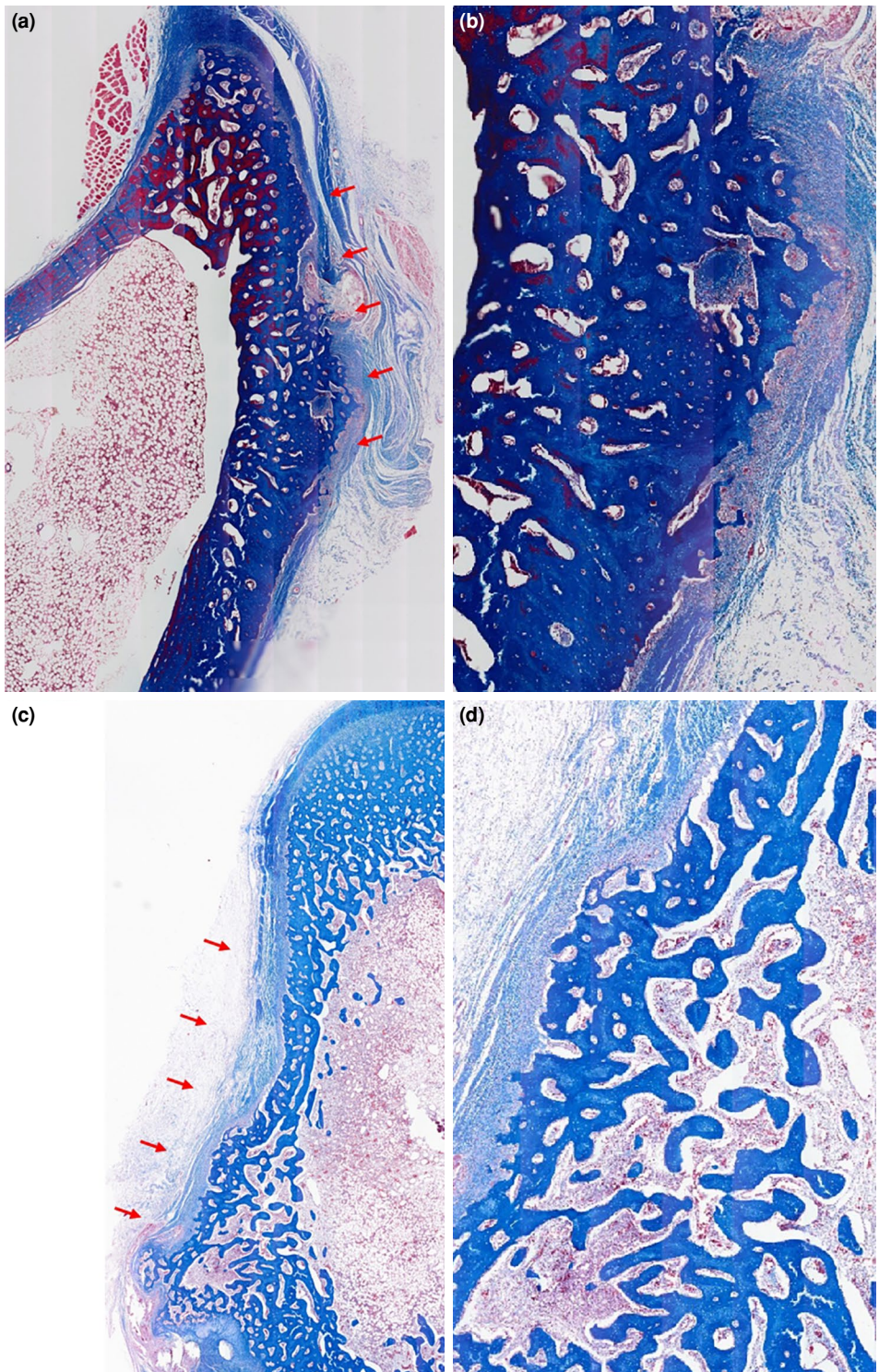

FIGURE 4. Masson's trichrome staining at 4 Weeks post-surgery. The specimen that received PRF grafting with periosteal repair **(a, b)** exhibited more tightly organized new bone formation than the specimen with only periosteal repair **(c, d)**, although the difference of the semi-quantitative histological score was not statistically significant. The red arrows indicate the bone defect area. B and D show magnified views of the corresponding regions (Masson's trichrome staining, ×20).

PRF, plasma-rich fibrin.

FIGURE 5. Micro-CT analysis at 8 Weeks post-surgery. Axial scan images. The specimen that received PRF grafting with periosteal repair **(a)** demonstrated the better quality of new bone formation than the specimen with only periosteal repair **(b)**. The white arrows indicate the bone defect area.

CT, computed tomography.

The PRP supposedly contributes to bone and tendon healing due to various mechanisms, including multiple growth factors, chemotaxis-induced cell migration, and angiogenic effects.[6,7,15-17] In clinical applications, PRP has been extensively studied for tendon healing in animal and human studies.[18,19] Dolkart et al.[20] reported that PRP administration during rotator cuff repair in rats improved the structural organization and mechanical strength of the healing bone-tendon interface, findings that have also been validated in clinical settings.[21] In contrast to the widespread research on PRP in tendon repair, its application in bone healing remains limited. Recent *in vitro* studies have explored the osteogenic potential of PRP, demonstrating that PRP, when combined with biofunctional scaffolds, promotes osteogenesis in controlled laboratory settings.[22-24] Additionally, several studies have reported that PRP enhances the osteogenic differentiation of amniotic fluid-derived stem cells and adipose-derived stem cells.[16,17,25] Based on this evidence, researchers have attempted to apply PRP clinically for bone defects in craniofacial or orthopedic surgery. However, the effectiveness of PRP for a bone defect of long bone still remains controversial within the orthopedic field.[26-28] A systematic review of PRP treatment for bone fractures concluded that although PRP demonstrated promising osteogenic potential in preclinical studies, these findings did not consistently translate into similar outcomes in clinical trials.[28] Conversely, some clinical studies reported improved healing rates in long bone non-union or delayed union when PRP was combined with autologous bone graft.[26,29] The discrepancies in reported outcomes regarding the osteogenic effects of PRP can be attributed to variations in application methods and treatment protocols across different studies.

To effectively use PRP for bone defects, several critical factors must be considered. First, PRP is a fluid, which poses challenges in maintaining its presence within the bone defect site for an extended period. To address this, a suitable scaffold is required, which can be achieved by incorporating a biomaterial scaffold or by inducing the coagulation of PRP.[21-23,30] Various techniques exist for converting PRP into PRF, including mixing PRP with 10% calcium gluconate or, as employed in the present study, combining it with thrombin to facilitate coagulation.[21,30] The thrombin-induced coagulation method is widely used in clinical studies on PRF for tendon repair and is particularly advantageous for clinical application due to the availability of commercial thrombin.[30] In the present study,

commercial human thrombin was used, as there was no available commercial rabbit thrombin. The PRF prepared using this method exhibited appropriate properties for grafting. Thus, fibrinization of PRP for bone defects, particularly in long bones, has the potential to enhance its practical clinical applicability. Second, various commercial PRP preparation kits by each providing their own preparation protocol yield PRP compositions with differing biological properties, leading to considerable variability in study outcomes.[6] Current evidence strongly recommends adherence to specific preparation methods to optimize PRP efficacy, including (1) double-spin centrifugation, (2) the use of a thick needle (> 21-gauge) for blood sampling, and (3) the generation of leukocyte-rich PRP.[31,32] In the present study, these guidelines were followed by using a PRP preparation kit designed to produce leukocyte-rich PRP via double-spin centrifugation.

In clinical practice, fibrinization of PRP might enhance its usability and effectiveness for treating bone defects. However, few studies have investigated the application of PRF, particularly in the bone defect of long bone. A previous animal study evaluated the osteogenic effects of PRF in a rat femoral bone defect model.[10] In the aforementioned study, PRF was prepared by mixing PRP with a 10% sodium chloride solution and implanted at the bone defect site, followed by periosteal repair. The results demonstrated superior bone healing in the PRF-treated group compared to periosteal repair alone. Despite these findings, the study was limited by using of rats, which are relatively small and might not provide an ideal model for a bone defect of long bone. A key strength of the present study is the use of rabbits, which offers a more appropriate model for bone defect formation of long bone. Another study used rabbits to investigate the osteogenic effect of PRF on a bone defect of femoral condyle. They created a round bone defect measuring 4 mm in diameter and 8 mm in depth, which is comparable to the defect size used in the present study. Although the study highlighted the osteogenic potential of PRF, its design compared PRF alone with PRF combined with a synthetic graft material, thereby emphasizing the effect of the combination rather than the intrinsic osteogenic potential of PRF itself.[33] In the present study, we compared PRF combined with periosteal repair with periosteal repair alone as control group, as the periosteum is known to play a crucial role in the healing process of fractures and bone defects.[10,34] To eliminate any bias arising from this, periosteal repair was performed in both groups.

Using an appropriate scaffold is a potential strategy for applying PRP to bone defect sites. Incorporating PRP into three-dimensional printed polylactic acid/gelatin-nano-hydroxyapatite scaffolds or vascularized biofunctional scaffolds enhances bone regeneration in both *in vitro* and animal studies.[22,23] Autologous bone also serves as an effective scaffold for PRP grafts. In a rabbit bone defect model, the combination of autologous bone particles and PRP demonstrated superior bone regeneration compared to PRP alone, as evidenced by histochemical and radiological analysis.[35] Furthermore, a clinical study involving 75 patients with long bone non-unions reported a higher bone healing rate, when PRP was combined with autologous iliac bone grafts than autologous bone grafts alone.[29] Currently, autologous iliac bone grafting remains the preferred treatment for large bone defects due to its osteogenic and osteoconductive properties. However, donor site morbidity is a significant limitation. Of note, PRF presents a promising alternative, as it not only provides osteogenic potential, but also exhibits appropriate properties for grafting to the bone defect site.

Nonetheless, this study has several limitations. First, the composition of PRP was not analyzed, preventing the determination of platelet concentration and growth factor content. However, the commercial PRP preparation kit used in this study has been validated in previous research, supporting the assumption that the PRP obtained was of appropriate quality.[21] Second, the study did not assess the extent to which PRF was retained at the bone defect site, despite this being a primary rationale for its use. Future research comparing PRF and PRP grafts in bone defect sites is necessary to evaluate retention efficacy. Third, since a PRP preparation kit designed for human use was employed in animal models, differences in platelet concentration between species raise concerns about the suitability of the PRP generated. Nevertheless, best-practice protocols, including double-spin centrifugation and the use of a thick needle, were followed to optimize PRP quality. Fourth, allogenic PRP was used, with PRP from a rabbit distributed among the others. While autologous PRP would have been preferable, the large volume of blood required for PRP preparation posed a mortality risk in individual rabbits. Finally, the sample size was small and no power analysis was performed

in the present study, potentially increasing the risk of a type 2 error. Although a larger sample size determined by a formal power analysis would have been ideal, the number of animals used in this study was minimized in accordance with ethical considerations and animal welfare guidelines. This study serves as a preliminary investigation into the feasibility of fibrinized PRP for bone defect treatment. Further larger-scale studies are required to validate these findings.

In conclusion, the PRF graft with periosteal repair appears to promote improved early-stage new bone formation in bone defects of long bone in an animal model compared to periosteal repair alone, although there was no statistically significant difference. Further research with a large sample size is required to more comprehensively assess the osteogenic effect of PRF.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: I.P.: Idea/concept, design, control/supervision, analysis and/or interpretation, writing the article, critical review; S.J., J.R.: Data collection and/or processing, materials; I.P., S.J., J.R.: Literature review, references and fundings.

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