Exp. Anim. 65(4), 473–483, 2016

—Original—

Comparison of the wound healing efficacy of polyglycolic acid sheets with fibrin glue and gelatin sponge dressings in a rat cranial periosteal defect model

Shinya KOSHINUMA[1)], Shoko MURAKAMI[1)], Masaharu NOI[1)], Takuya MURAKAMI[1)], Ken-Ichi MUKAISHO[2)], Hiroyuki SUGIHARA[2)], and Gaku YAMAMOTO[1)]

[1)]*Department of Oral and Maxillofacial Surgery, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga 520-2192, Japan*
[2)]*Department of Pathology, Division of Molecular Diagnostic Pathology, Shiga University of Medical Science, Japan*

Abstract: Oral surgical procedures occasionally require removal of the periosteum due to lesions, and these raw bone surfaces are prone not only to infection but also to scar formation during secondary healing. The objective of this study was to identify successful methods for reconstruction using periosteal defect dressings. We created 1-cm^2 defects in the skin and cranial periosteum of 10-week-old male Wistar rats under isoflurane anesthesia. The animals were assigned to three defect treatment groups: (1) polyglycolic acid sheets with fibrin glue dressing (PGA-FG), (2) Spongel® gelatin sponge dressing (GS), and (3) open wound (control). Postoperative wound healing was histologically evaluated at 2, 4, and 6 weeks. The moist conditions maintained by the GS and PGA-FG treatments protected the bone surface from the destructive effects of drying and infection. Complete wound healing was observed in the GS group but not for all animals in the PGA-FG and control groups. Histologically, osteoblast proliferation on bone surfaces and complete epithelialization with adnexa were observed in the GS group at 6 weeks after surgery. In contrast, PGA sheets that had not been absorbed inhibited osteoblast proliferation and delayed wound healing in the PGA-FG group. Wound surface dressings maintain a moist environment that promotes wound healing, but PGA materials may not be suitable for cases involving exposed periosteum or bone surfaces due to the observed scar formation and foreign-body reaction.

Key words: dressing material, osteoblast, periosteum, wound healing

Introduction

Surgical procedures in the oral cavity occasionally result in exposure of the bone, and this is particularly true in cases involving partial resection of soft tissues due to oral cancers or precancerous lesions. These procedures include vestibuloplasty for preprosthetic treatments and resection of broad mucosal lesions in the gingival and alveolar areas [28]. When removal of the periosteum is required, adequately dressing the bone surface may be problematic. Raw bone surfaces in the oral cavity are prone to not only infection but also to scar formation during secondary healing, and proper covering of the exposed periosteum or bone surface is often necessary to prevent these complications [5, 6]. Mucosal and skin autografts have been used for this

(Received 22 March 2016 / Accepted 15 June 2016 / Published online in J-STAGE 5 July 2016)
Address corresponding: S. Koshinuma, Department of Oral and Maxillofacial Surgery, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga 520-2192, Japan

purpose, but these grafts require a separate surgical procedure and are associated with other disadvantages [1, 2, 23, 28, 29].

Since the early 1980s, several new dressing materials have been developed in an effort to promote wound healing [19]. The ideal dressing needs to ensure that the wound remains moist with exudate [19]. In this study, we evaluated two different dressing materials: polyglycolic acid (PGA) sheets with fibrin glue (FG) and the gelatin sponge (GS). PGA sheets are hydrolyzed *in vivo*, with subsequent degradation and absorption, and their coating effect is known to be enhanced if they are applied in combination with FG [24]. This combined PGA-FG therapy has been widely used in multiple surgical fields, and several studies have reported on its safety and efficacy [7, 9, 25–27]. In addition, PGA-FG composites have been utilized as sealants during orthopedic surgery and as a means of achieving hemostasis during liver and pancreatic surgery [31]. This has also been attempted in surgical repairs following oral tumor resection, and this approach has been reported to be useful for maintaining postoperative quality of life in patients after partial tongue resection [15]. However, it has not been reported that PGA sheets possess any bioactive properties that induce osteogenesis. Therefore, the effectiveness of PGA sheets in covering denuded bone surfaces remains unclear.

GS is a water-insoluble hemostatic agent composed of bovine or porcine collagen [14]. Although GS is extracted from the bovine or porcine dermis, there is little risk of rejection. Because it is applied as antigenic extremely low nature polymer materials which purified an antigenic strong telopeptide moiety after digestion, the removal in protease such as the pepsin highly [21]. This agent was first used for surgical hemostasis in 1945, and it is commonly used to promote blood coagulation [4, 8]. Due to the water absorption capability of its hydrophilic structure, GS has also been used as a scaffold for mesenchymal stem cells and as a medium for the controlled release of growth factors [17] as well as differentiation and induction factors [10]. In the field of oral and maxillofacial surgery, GS has been used in the past to cover extraction sockets [3]. The collagen not only induces platelet adhesion but also stimulates platelet aggregation. It also has the ability to protect tissues from chemicals, heat, and bacterial infection, and reduced pain has been reported with its use as a wound cover [11].

The periosteum is a fibrous and highly vascularized tissue layer that is firmly attached to the outer surface of bones. Histologically, it is divided into an inner cambium layer in contact with the bone and an outer fibrous layer. The former is characterized by a high density of osteoblasts and pre-osteoblasts, whereas the latter contains fibroblasts. Although the bone cortex is the main beneficiary of the principal anatomical and physiological functions of the periosteal membrane, the activity of the periosteum influences the behavior of the entire bone [13]. Most importantly, the periosteum participates in osteogenesis, serves as an attachment site for muscles and ligaments, and supplies blood to the cortical bone [12, 22]. Apart from its nutritive functions, the periosteum also has a mechanical function and plays an important role in tissue repair. Following surgical treatment of osseous defects, the periosteum is thought to be of paramount importance in the healing process [18, 30].

Because the main purpose of the present study was to examine osteogenesis and wound healing secondary to periosteum reproduction in a moist environment, we used a rat cranial periosteal defect model, as this kind of defect can be easily created and observed during an experimental period.

Materials and Methods

Animals

We used thirty-six 10-week-old male Wistar rats (CLEA Japan, Inc., Tokyo, Japan) in this study. The rats were divided into three treatment groups: PGA sheets with fibrin glue dressing (PGA-FG), Spongel® gelatin sponge dressing (GS), and open wound (control). Because wounds are sometimes left open in human intraoral operation cases, to form the bone into a dish form because of expected self-purification, the defects in the skin and cranial periosteum were left open, i.e., without dressings, in the control animals.

Twelve animals were assigned to each group. Animals were housed at the Research Center for Animal Life Science, Shiga University of Medical Science, and maintained in a temperature- and humidity-controlled (23 ± 1°C, 60 ± 10%) environment. During the experimental period, rats were given free access to water and CLEA Rodent Diet CE-2 (CLEA Japan, Inc., Tokyo, Japan). This study received approval from the Shiga University of Medical Science animal experimental ethics committee (experimental plan approval number 2013–3-11), and we conducted this study in accordance with the Shiga

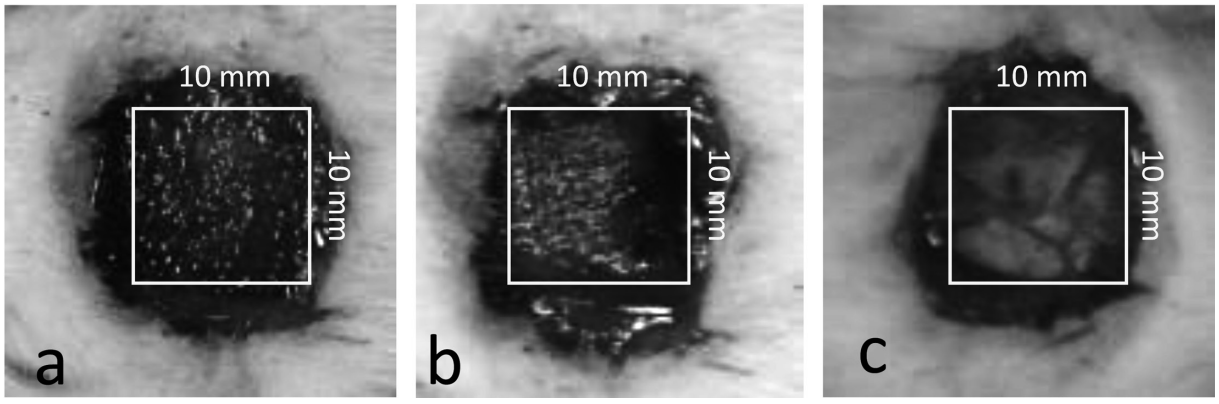

Fig. 1. Representative photographs of defects in the skin and cranial periosteum in each group. a) PGA-FG group, b) GS group, and c) control group. A 1-cm^2 defect (surrounded by a yellow square) in the skin and cranial periosteum was created in the parietal region of the skull of each rat. After that, we applied PGA sheets combined with FG or a GS dressing for rat cranial periosteum defect repair (a and b). We did not cover the defect with any dressing materials in the control group (c).

University of Medical Science guidelines for animal experiments and the Act on Welfare and Management of Animals.

Implant materials

A 1-cm^2 defect in the skin and cranial periosteum was created in the parietal region of the skull of each rat. The rats were divided into three different treatment groups (PGA-FG, GS, and control), with twelve rats assigned to each group. We used a Spongel® GS dressing with an isoelectric point of 4.9 and a weight average molecular weight of 99,000 (Astellas Pharma. Inc., Tokyo, Japan) and PGA sheets (Neoveil, Gunze Ltd., Osaka, Japan) combined with FG (Bolheal, Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) for rat cranial periosteum defect repair. Because the quality of a GS and PGA sheets can be preserved for a long time, we could perform the experiments for 6 weeks without changing them.

Operative procedure

All rats were fasted for 24 h prior to the surgical procedure. The rats were placed in a plastic box configured for delivery of general anesthesia (isoflurane 3–5%, flow rate 5.0 l/min), and we then shaved and disinfected the surgical site. The skin and subcutaneous tissue were incised in the parietal region to create one 1 cm side of the quadrangle defect, and the periosteum was exfoliated using a curette to expose the bone (Fig. 1). After the surgery, we bred a rat in each gauge to prevent a wound from touching. Tetracycline hydrochloride (18 mg/day/body) was mixed with tap water and administered orally for 5 days.

Macroscopic findings

The calvarial wounds in each group were photographed, and the wound aspects were evaluated using the ImageJ software (National Institutes of Health, Bethesda, MA, USA). The defect area of the periosteum and skin was measured in all animals using these photographs.

Histological examination

The rats were sacrificed by cervical dislocation under general anesthesia using isoflurane. Calvarial tissue samples were collected from animals in each group. The tissue samples were fixed in 10% formalin for 7 days. To make sectioning easier for staining of tissue including the bone, the samples were decalcified in EDTA solution for 7 days and then embedded in paraffin. Three-micrometer sections were cut and stained with hematoxylin and eosin (H&E). Bone remodeling, wound healing, and the location of osteoblasts lining the defect were evaluated. The calvarial bone thickness of each sample was measured in 10 randomly selected microscope image fields.

Statistical analyses

Because of the relatively small number of animals included in the present study, we combined 4- and 6-week data in our comparison of the three different groups. Statistical analyses were performed using analysis of covariance. The level of significance of the official approval assumed it both sides 1.7 (=5/3)%.

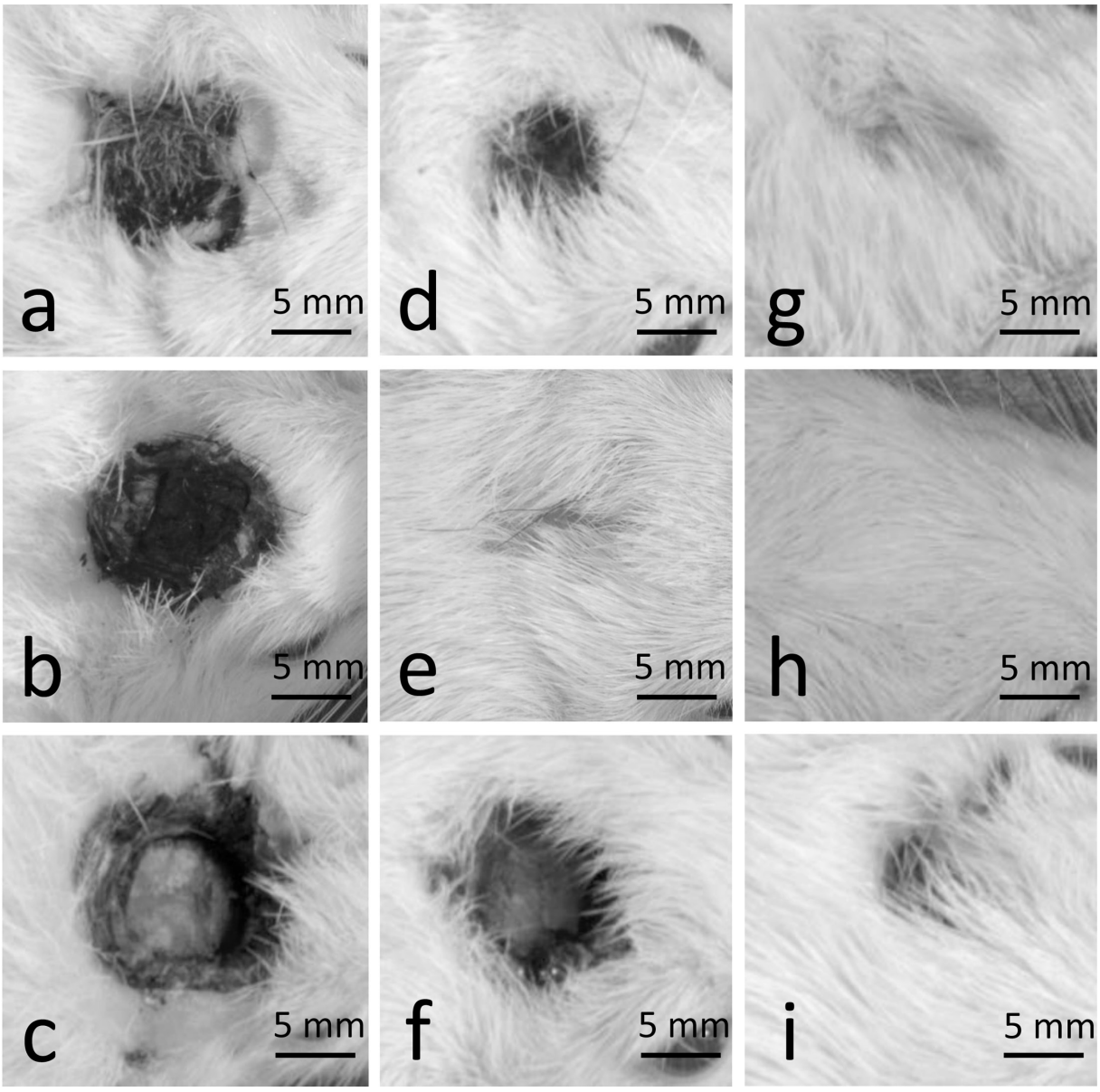

Fig. 2. Representative photographs of macroscopic findings. The progression of postsurgical healing in the PGA-FG (a, d, g), GS (b, e, h), and control groups (c, f, i) observed at 2 weeks (a, b, c), 4 weeks (d, e, f), and 6 weeks (g, h, i). Complete wound healing occurred earlier in the GS group than in the other groups (g, h, i).

Results

Macroscopic findings in each treatment group

Representative images of the postsurgical healing process in each group at 2, 4, and 6 weeks are shown in Fig. 2. At 2 weeks after surgery, there were no remarkable differences in wound area reduction among the groups, and the wound was still open in all cases. However, there were differences in the condition of the bone surfaces. The wound was covered with a blood clot in

Table 1. Summary of measurements of the wound surface defect area

	2 weeks	4 weeks	6 weeks
PGA-FG	66.5 ± 15.5	71.2 ± 25.3	5.0 ± 7.0
GS	79.8 ± 23.3	47.6 ± 47.3	–
Control	90.4 ± 11.2	75.3 ± 10.6	62.3 ± 30.0

The data are shown as mean ± standard deviation (mm^2).

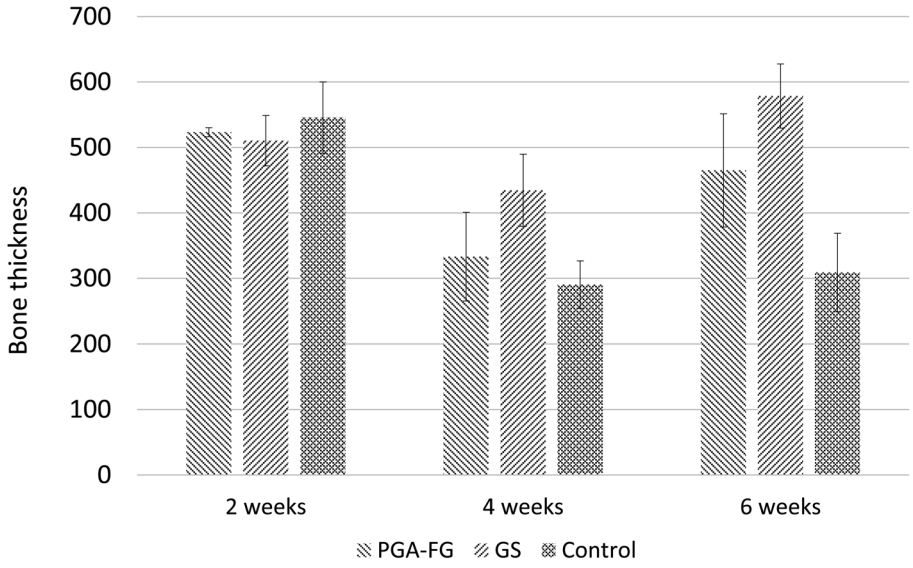

Fig. 3. Changes in cranial bone thickness. The postsurgical cranial bone thickness at 4 weeks was much lower than that at the 2-week time point in all groups, and this was particularly pronounced in the control group. In the GS and PGA-FG groups, cranial bone thickness was restored 6 weeks after surgery. However, recovery of cranial bone thickness was not observed in the control group. GS group, red bar; PGA-FG group, blue bar; control group, green bar.

both the GS and PGA-FG groups (Figs. 2a and 2b). In contrast, raw bone was exposed and in a dry condition in the control group (Fig. 2c). At 4 weeks after surgery, the GS group exhibited greater promotion of wound healing as compared with the other groups (Figs. 2d and 2f, respectively). Although there were no rats that showed complete wound closure with skin regeneration in either the PGA-FG or control groups, there was one rat with complete wound closure at 4 weeks in the GS group (Fig. 2e). At 6 weeks after surgery, the wounds in all GS group rats were closed, with complete epithelialization and hair coverage of the wound surface (Fig. 2h). However, 25% and 75% of the wounds were still open in the PGA-FG and control rats, respectively (Figs. 2g and 2i).

Measurement of the wound surface defect area

Measurements of the wound surface defect area are summarized in Table 1. The data were expressed as the mean ± standard deviation (SD). At 2 weeks after surgery, the defect areas were 66.5 ± 15.5 mm^2, 79.8 ± 23.3 mm^2, and 90.4 ± 11.2 mm^2 in the PGA-FG, GS, and control groups, respectively. At the 4-week evaluation, the defect areas were 71.2 ± 25.3 mm^2, 47.6 ± 47.3 mm^2, and 75.3 ± 10.6 mm^2 in the PGA-FG, GS, and control groups, respectively. At 6 weeks after surgery, all GS rats exhibited complete epithelialization, and there was no measurable defect area in this group. In contrast, the defect areas in the PGA-FG and control groups were 5.0 ± 7.0 mm^2 and 62.3 ± 30.0 mm^2, respectively.

Cranial bone thickness

We measured the calvarial bone thickness in 10 randomly selected microscope image fields in the H&E-stained tissue sections. The observed bone surface irregularities were more severe in the control group than in the other groups. Figure 3 shows the changes in cranial bone thickness for each group during the experimental period. The postsurgical bone thickness was much lower at 4 weeks than at 2 weeks in all groups, and the reduction was most significant in the control group. Bone resorption worsened during this period because we exfoliated the periosteum, which plays an important role in bone regeneration.

The cranial bone thickness measurements were expressed as the mean ± SD. The average bone thickness in the 10-week-old Wistar rats not subjected to the surgical procedure was 491.8 ± 25.7 μm. The postsurgical cranial bone thicknesses at 2 weeks were 523.2 ± 8.0 μm, 497.4 ± 50.5 μm, and 535.3 ± 59.4 μm in the PGA-FG, GS, and control groups, respectively. No significant differences were observed between the experimental groups. At 4 weeks after surgery, the GS rats exhibited

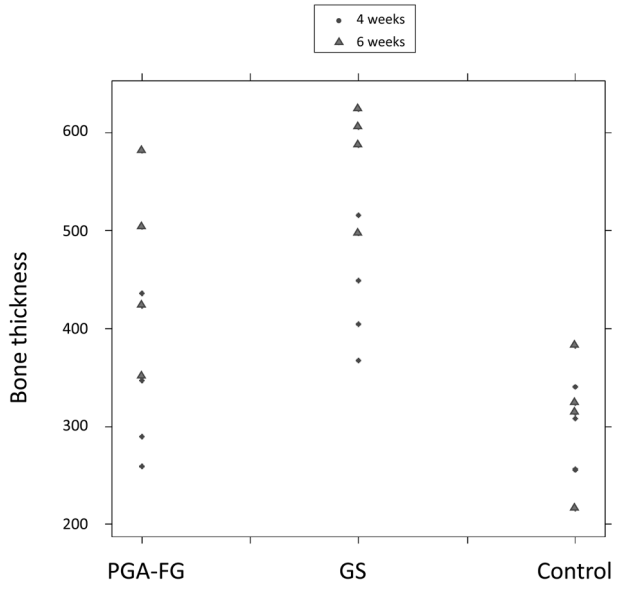

Fig. 4. Scatter plot of postsurgical cranial bone thickness at 4 and 6 weeks. Calvarial bone thickness measurements at 4 and 6 weeks plotted for each treatment group. Blue and red dots indicate the postsurgical thickness values at 4 and 6 weeks, respectively. There was a statistically significant increase in cranial bone thickness in the GS group as compared with the PGA-FG (*P=0.0085*) and control (*P=0.00002*) groups.

the thickest cranial bone (429.8 ± 63.0 μm). The bone thicknesses in the PGA-FG and control animals were 357.9 ± 60.3 μm and 284.6 ± 40.0 μm, respectively. Similarly, at 6 weeks post surgery, the cranial bone thickness measurements were highest in the GS treatment group (569.5 ± 53.5 μm). The PGA-FG and control groups were found to have bone thicknesses of 503.0 ± 64.9 μm and 360.7 ± 135.6 μm, respectively.

A scatter plot of cranial bone thickness at 4 and 6 weeks following surgery for each treatment group is shown in Fig. 4. A linear regression analysis was performed to assess any effects of dressing type on cranial bone remodeling. The GS treatment group exhibited a statistically significant increase in cranial bone thickness as compared with the PGA-FG (*P=0.0085*) and control (*P=0.00002*) groups.

Histological findings

Representative photomicrographs of tissue sections from each group at 2, 4 and 6 weeks are shown in Figs. 5–7, respectively. At 2 weeks after surgery, the defect area was covered by dressing materials and an associated blood clot in the GS and PGA-FG groups (Figs. 5a–5d). However, in the control group, the exposed bone was mostly dry (Figs. 5e and 5f). Mild irregularities on the bone surface under the influence of this drying were detected in the control group (Figs. 5e and 5f). At 4 weeks after surgery, most of the defect area in the PGA-FG group was open because the PGA sheets were still in place and had not been absorbed (Figs. 6a and 6b). On the other hand, one rat in the GS group had complete wound closure, with the wound covered by thin skin with incomplete adnexa. We identified osteoblasts lining the surface of the bone in this GS group rat (Figs. 6c and 6d). In the control group, we detected severe irregularities on the bone surface as a result of secondary infection (Figs. 6e and 6f). At 6 weeks after surgery, the PGA-induced foreign-body reaction resulted in an almost complete absence of osteoblasts lining the bone surfaces in the PGA-FG group, and partial hair follicles were detected in most parts of the dermis (Figs. 7a and 7b). In contrast, complete epithelialization with hair follicle formation was observed in the GS group, and minimal bone surface irregularities were noted (Fig. 7c). We also identified osteoblasts lining the surface of the bone in the GS group (Fig. 7d). Although there were areas covered by thin skin with incomplete adnexa at the edge of defect area in the control group, the resected tissues were mostly replaced by inflammatory granulation tissue containing numerous small vessels and inflammatory cells. No osteoblasts lining the bone surfaces were detected in most parts of the defect area (Figs. 7e and 7f).

Discussion

The present study demonstrated the wound healing efficacy of PGA-FG and GS treatments as compared with the control in a rat cranial periosteal defect model. The findings of this study are consistent with the results of previous studies demonstrating the necessity of using a biomaterial as a means of maintaining a moist environment in the region of bone exposure in cases involving wide mucous membrane loss [2, 19, 20, 28, 29]. Since the combination of PGA sheets and FG has been widely used in multiple surgical fields, we expected the PGA-FG treatment to promote better wound healing than the other groups. However, the GS treatment exhibited better promotion of bone remodeling with osteoblasts lining the bone surface than the PGA-FG treatment. The delay in wound healing and inhibition of osteoblast prolifera-

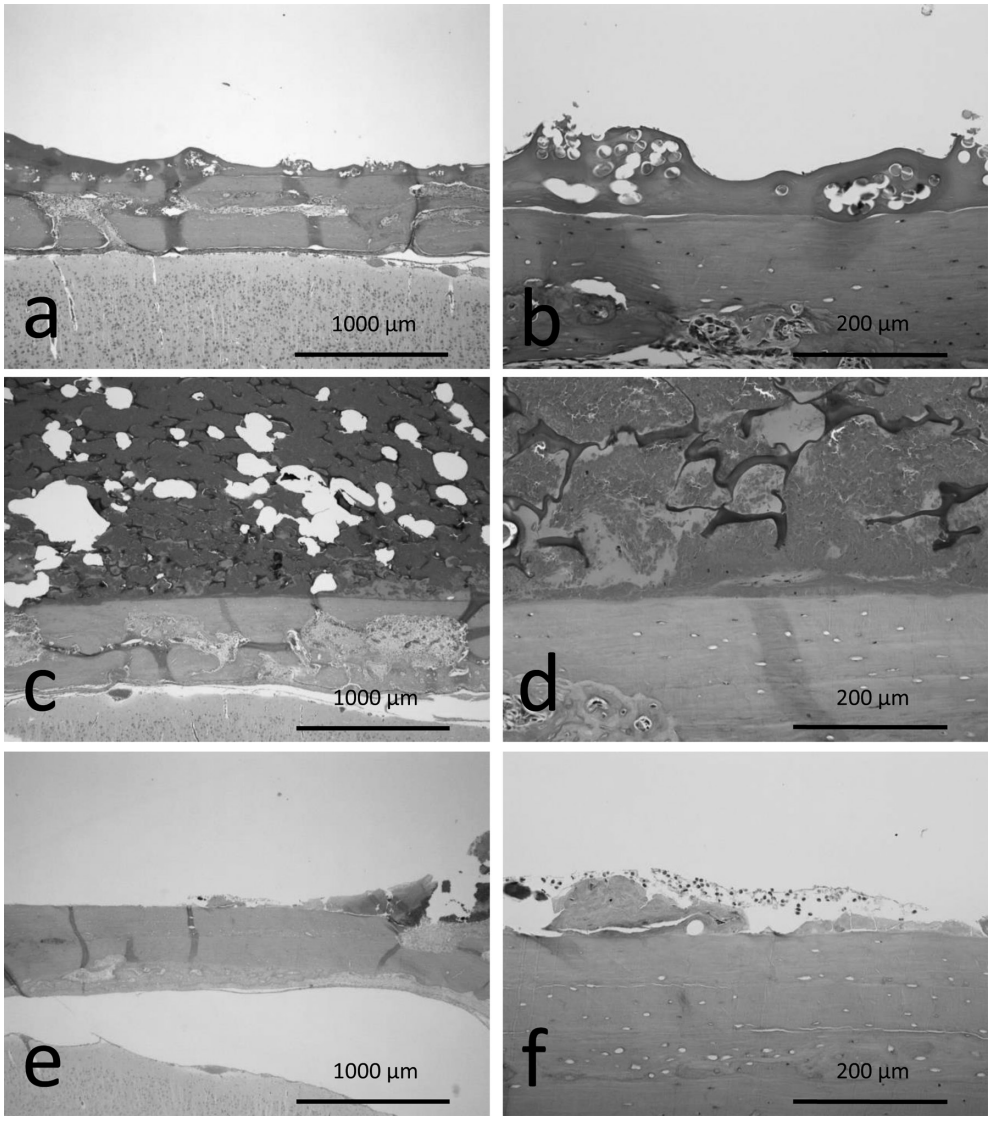

Fig. 5. Representative photomicrographs of tissue sections from each group at 2 weeks after surgery. (a, b) PGA-FG group, (c, d) GS group, and (e, f) control group. B, d, and f are higher magnification versions of a, c, and e, respectively. The bone surface in the defect area was smooth and covered by dressing materials and an associated blood clot in the PGA-FG and GS groups (a–d). However, mild irregularities on the bone surface under the influence of the drying were detected in the control group (e and f).

tion observed in the PGA-FG group was because the PGA sheets had not been absorbed and scar formation and a foreign-body reaction to the PGA sheet material had occurred. These findings suggest that PGA sheets are not suitable for use in cases involving a periosteal defect.

Gelatin can be used in small regions of mucoperiosteal loss, such as extraction sockets. However, in cases involving loss of larger areas of the mucoperiosteum, it is difficult to retain gelatin over the defect due to its tendency to liquefy. It has been reported that materials that resist *in vivo* degradation are superior for space-occupying applications and that materials that promote cellular infiltration are superior in terms of inducing cell properties associated with wound healing [20]. Other investigators have shown that GS is absorbed in 4 weeks, whereas PGA sheets are absorbed by hydrolysis and metabolic activity within approximately 15 weeks [16]. In the present study, the PGA sheets were in place for a longer duration as compared with the GS materials, and

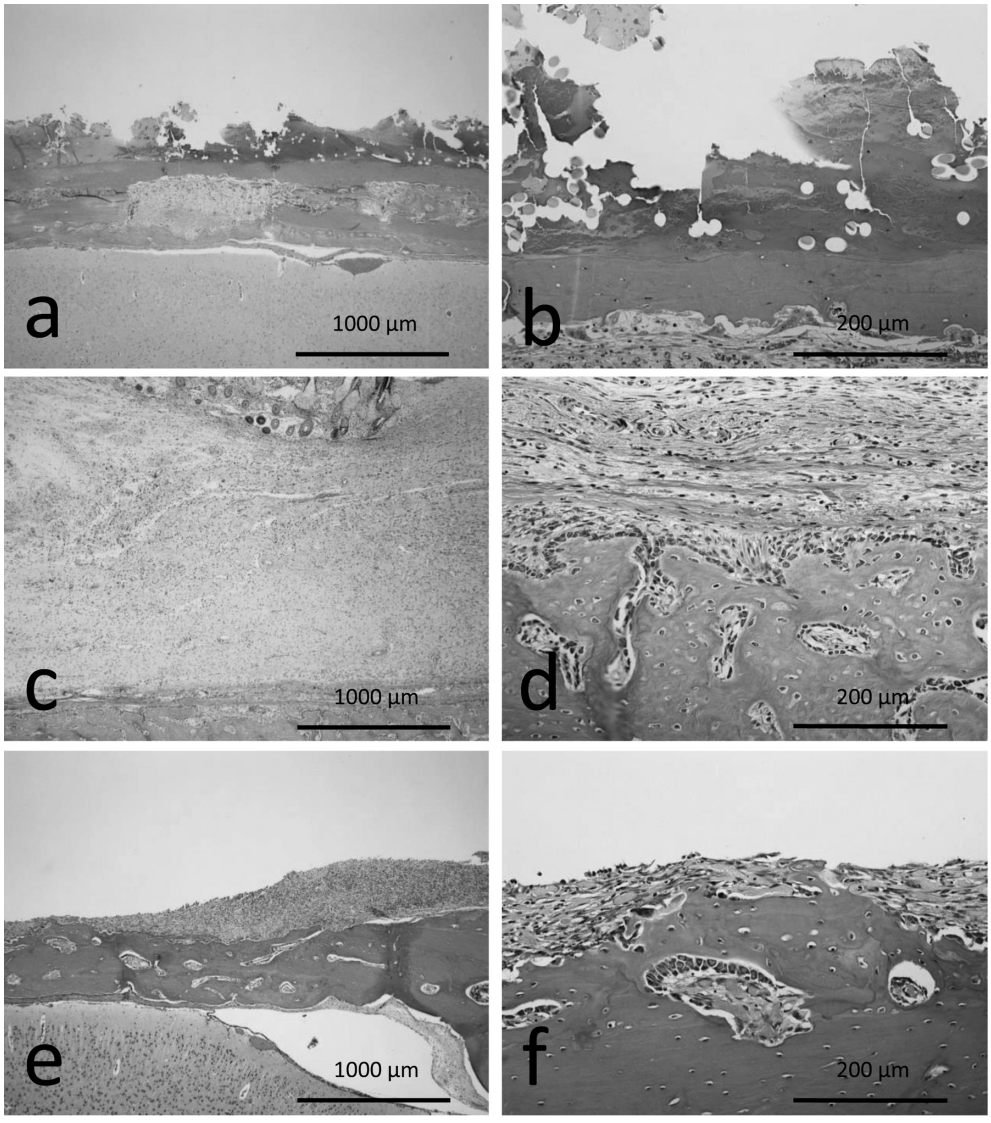

Fig. 6. Representative photomicrographs of tissue sections from each group at 4 weeks after surgery. (a, b) PGA-FG group, (c, d) GS group, and (e, f) control group. B, d, and f are higher magnification version of a, c, and e respectively. The PGA sheets were still in place and had not been absorbed (a and b). Complete wound closure, with the wound covered by thin skin with incomplete adnexa, was observed in a rat in the GS group (c). We identified osteoblasts lining the surface of the bone in this GS group rat (d). The resected tissues were mostly replaced by inflammatory granulation tissue in the control group (e and f).

PGA-induced scar formation and a foreign-body reaction were observed at 6 weeks after surgery. PGA sheets that have not been absorbed may inhibit periosteum formation and osteoblast proliferation and thereby delay bone remodeling and ultimately wound healing. The present experimental study suggests that the GS treatment results in better promotion of bone remodeling, as demonstrated by osteoblasts lining the bone surface, than the PGA-FG treatment in the case of 1-cm^2 defects in the skin and cranial periosteum. If GS materials could cover wider defects in human cases, GS treatment could also be considered to result in better wound healing than PGA-FG treatment, similar to the present results. However, there are currently no GS materials available that are capable of adhering to a broad wound involving bone exposure long enough for epithelialization to occur. Based on the present results, we might consider use of a PGA-FG composite initially for maintaining moist conditions in

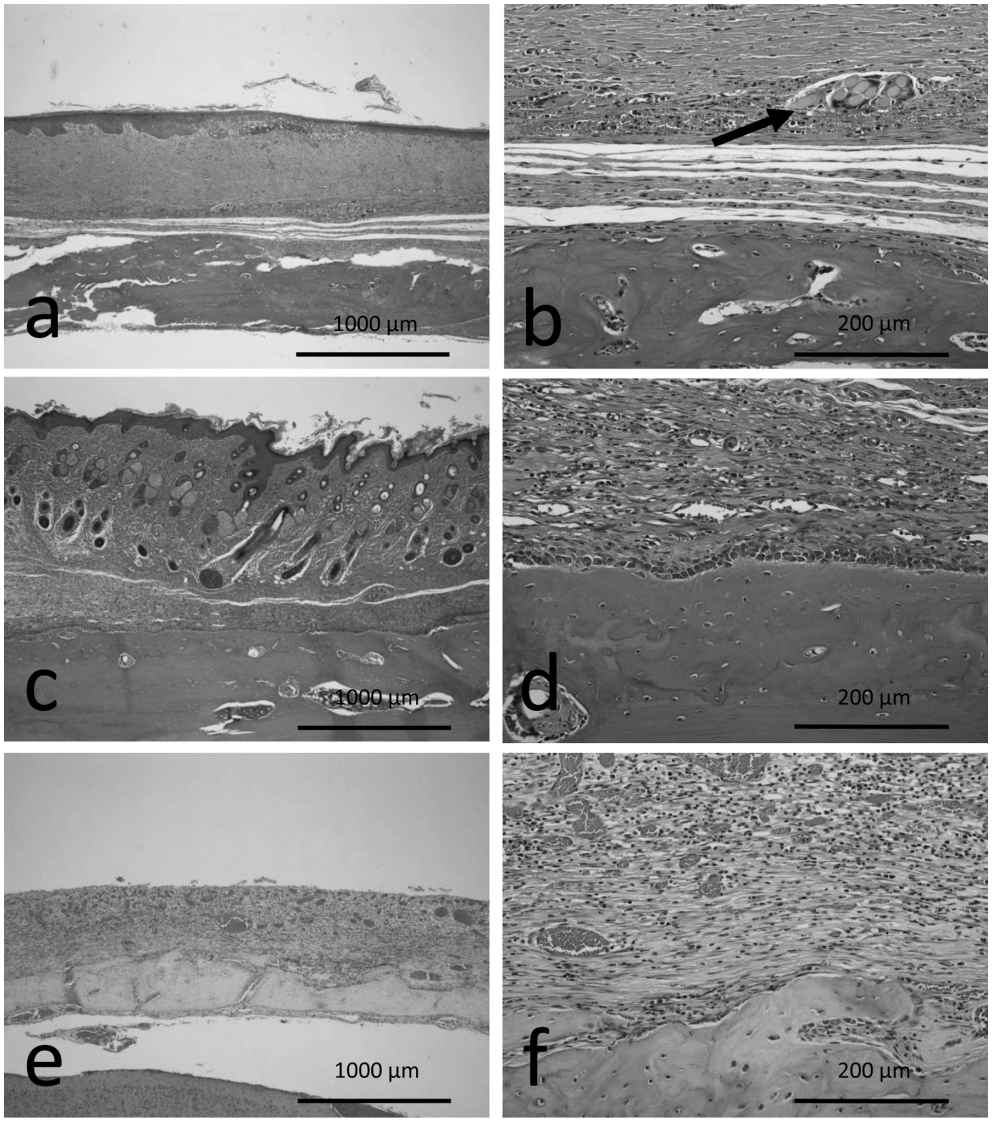

Fig. 7. Representative photomicrographs of tissue sections from each group at 6 weeks after surgery. (a, b) PGA-FG group, (c, d) GS group, and (e, f) control group. B, d, and f are higher magnification versions of a, c, and e respectively. Thin epithelialization without any hair follicles was detected in most of the dermis in the PGA-FG group (a). Foreign-body reactions (black arrow) to the PGA sheets were observed (b). Complete epithelialization with hair follicles was observed, and osteoblasts lining the surface of the bone were clearly seen in the GS group (c and d). The resected tissues were mostly replaced by inflammatory granulation tissue containing numerous small vessels and inflammatory cells (e and f).

cases with a broad wound defect and removal of it before a foreign-body reaction occurs.

In summary, it is important to cover the entire defect surface when treating a wound involving bone exposure in order to maintain a moist environment. Any biomaterial applied as a wound surface covering must not inhibit osteoblast proliferation. Although development of biomaterials has advanced medical treatment, we are often faced with challenging wounds involving bone exposure in oral and maxillofacial surgery. Therefore, we need biomaterials that completely cover the wound surface and exhibit rapid *in vivo* resorption. As rats were used in this study, it is necessary to pursue further investigations in a larger animal model.

Acknowledgment

The authors would like to thank Professor Takashi OMORI (Department of Social/Community Medicine and Health Science, Faculty of Biomedical Sciences, School of Medicine, Kobe University, and Center for Clinical Research, Kobe University Hospital) for performing the statistical analysis.

Reference

1. Bie, T., Aarnes, K., and Bang, G. 1980. Split thickness skin graft for vestibuloplasty operations. *Int. J. Oral Surg.* 9: 439–443. [Medline] [CrossRef]
2. Coslet, J.G., Rosenberg, E.S., and Tisot, R. 1980. The free autogenous gingival graft. *Dent. Clin. North Am.* 24: 651–682. [Medline]
3. Ding, X., Takahata, M., Akazawa, T., Iwasaki, N., Abe, Y., Komatsu, M., Murata, M., Ito, M., Abumi, K., and Minami, A. 2011. Improved bioabsorbability of synthetic hydroxyapatite through partial dissolution-precipitation of its surface. *J. Mater. Sci. Mater. Med.* 22: 1247–1255. [Medline] [CrossRef]
4. Evans, B.E. 1977. Local hemostatic agents. *N. Y. J. Dent.* 47: 109–114. [Medline]
5. Fröschl, T. and Kerscher, A. 1997. The optimal vestibuloplasty in preprosthetic surgery of the mandible. *J. Craniomaxillofac. Surg.* 25: 85–90. [Medline] [CrossRef]
6. Hillerup, S., Hopkins, R., and Koomen, H.A.1984. Mandibular vestibuloplasty. A review of clinical follow-up. p59–65. *In*: Proceedings Consensus Conference. The relative roles of vestibuloplasty and ridge augmentation in the management of the atrophic mandible (Stoelinga, P.J.W. ed.). Quintessence, Chicago.
7. Hayashibe, A., Sakamoto, K., Shinbo, M., Makimoto, S., and Nakamoto, T. 2006. New method for prevention of bile leakage after hepatic resection. *J. Surg. Oncol.* 94: 57–60. [Medline] [CrossRef]
8. Jenkins, H.P. and Janda, R. 1946. Studies on the Use of Gelatin Sponge or Foam as an Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins. *Ann. Surg.* 124: 952–961. [CrossRef]
9. Kawai, H., Harada, K., Ohta, H., Tokushima, T., and Oka, S. 2012. Prevention of alveolar air leakage after video-assisted thoracic surgery: comparison of the efficacy of methods involving the use of fibrin glue. *Thorac. Cardiovasc. Surg.* 60: 351–355. [Medline] [CrossRef]
10. Kim, J.C., Choi, S.S., Wang, S.J., and Kim, S.G. 2006. Minor complications after mandibular third molar surgery: type, incidence, and possible prevention. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 102: e4–e11. [Medline] [CrossRef]
11. Kim, S.G., Jeong, J.H., Che, X., Park, Y.T., Lee, S.W., Jung, E.S., Choe, S., and Choi, J.Y. 2013. Reconstruction of radial bone defect using gelatin sponge and a BMP-2 combination graft. *BMB Rep.* 46: 328–333. [Medline] [CrossRef]
12. Kowalski, M.J., Schemitsch, E.H., Kregor, P.J., Senft, D., and Swiontkowski, M.F. 1996. Effect of periosteal stripping on cortical bone perfusion: a laser doppler study in sheep. *Calcif. Tissue Int.* 59: 24–26. [Medline] [CrossRef]
13. Landry, P.S., Marino, A.A., Sadasivan, K.K., and Albright, J.A. 2000. Effect of soft-tissue trauma on the early periosteal response of bone to injury. *J. Trauma* 48: 479–483. [Medline] [CrossRef]
14. Loffroy, R., Guiu, B., Cercueil, J.P., and Krausé, D. 2009. Endovascular therapeutic embolisation: an overview of occluding agents and their effects on embolised tissues. *Curr. Vasc. Pharmacol.* 7: 250–263. [Medline] [CrossRef]
15. Maniwa, T., Kaneda, H., and Saito, Y. 2009. Management of a complicated pulmonary fistula caused by lung cancer using a fibrin glue-soaked polyglycolic acid sheet covered with an intercostal muscle flap. *Interact. Cardiovasc. Thorac. Surg.* 8: 697–698. [Medline] [CrossRef]
16. Miyayama, S., Yamakado, K., Anai, H., Abo, D., Minami, T., Takaki, H., Kodama, T., Yamanaka, T., Nishiofuku, H., Morimoto, K., Soyama, T., Hasegawa, Y., Nakamura, K., Yamanishi, T., Sato, M., and Nakajima, Y. 2014. Guidelines on the use of gelatin sponge particles in embolotherapy. *Jpn. J. Radiol.* 32: 242–250. [Medline] [CrossRef]
17. Omata, K., Matsuno, T., Asano, K., Hashimoto, Y., Tabata, Y., and Satoh, T. 2014. Enhanced bone regeneration by gelatin-β-tricalcium phosphate composites enabling controlled release of bFGF. *J. Tissue Eng. Regen. Med.* 8: 604–611. [Medline] [CrossRef]
18. Ortak, T., Ozdemir, R., Uysal, A., Ulusoy, M.G., Sungur, N., Sahin, B., Koçer, U., and Sensöz, O. 2005. Osteogenic capacities of periost grafts, periost flaps and prefabricated periosteal flaps: experimental study. *J. Craniofac. Surg.* 16: 594–600. [Medline] [CrossRef]
19. Paddle-Ledinek, J.E., Nasa, Z., and Cleland, H.J. 2006. Effect of different wound dressings on cell viability and proliferation. *Plast. Reconstr. Surg.* 117:(Suppl): 110S–118S, discussion 119S–120S. [Medline] [CrossRef]
20. Purna, S.K. and Babu, M. 2000. Collagen based dressings--a review. *Burns* 26: 54–62. [Medline] [CrossRef]
21. Rooney, P., Grant, M.E., and McClure, J. 1992. Endochondral ossification and de novo collagen synthesis during repair of the rat Achilles tendon. *Matrix* 12: 274–281. [Medline] [CrossRef]
22. Rücker, M., Binger, T., Deltcheva, K., and Menger, M.D. 2005. Reduction of midfacial periosteal perfusion failure by subperiosteal versus supraperiosteal dissection. *J. Oral Maxillofac. Surg.* 63: 87–92. [Medline] [CrossRef]
23. Sezer, B., Selçuk, E., Ertürk, S., and Gomel, M. 2004. Comparison of autogenous mucosal grafts and collagen-based, solvent-preserved allografts for vestibuloplasty. *Quintessence Int.* 35: 234–239. [Medline]
24. Shinya, N., Oka, S., Miyabashira, S., Kaetsu, H., Uchida, T., Sueyoshi, M., Takase, K., Akuzawa, M., Miyamoto, A., and Shigaki, T. 2009. Improvement of the tissue-adhesive and sealing effect of fibrin sealant using polyglycolic acid felt. *J. Invest. Surg.* 22: 383–389. [Medline] [CrossRef]
25. Takao, T., Takegawa, Y., Shinya, N., Tsudomi, K., Oka, S., and Ono, H. 2015. Tissue shielding with polyglycolic acid

sheets and fibrin glue on ulcers induced by endoscopic submucosal dissection in a porcine model. *Endosc. Int. Open* 3: E146–E151. [Medline] [CrossRef]

26. Takeuchi, J., Suzuki, H., Murata, M., Kakei, Y., Ri, S., Umeda, M., and Komori, T. 2013. Clinical evaluation of application of polyglycolic acid sheet and fibrin glue spray for partial glossectomy. *J. Oral Maxillofac. Surg.* 71: e126–e131. [Medline] [CrossRef]
27. Terasaka, S., Iwasaki, Y., Shinya, N., and Uchida, T. 2006. Fibrin glue and polyglycolic Acid nonwoven fabric as a biocompatible dural substitute. *Neurosurgery* 58 (Suppl): ONS134–ONS139, discussion ONS134–ONS139. [Medline]
28. Tsuno, H., Arai, N., Sakai, C., Okabe, M., Koike, C., Yoshida, T., Nikaido, T., and Noguchi, M. 2014. Intraoral application of hyperdry amniotic membrane to surgically exposed bone surface. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* 117: e83–e87. [Medline] [CrossRef]
29. Ueda, M., Kaneda, T., Oka, T., and Torii, S. 1984. Experimental study of dermal grafts for reconstruction of oral mucosa. *J. Oral Maxillofac. Surg.* 42: 213–223. [Medline] [CrossRef]
30. Utvåg, S.E., Grundnes, O., and Reikeraos, O. 1996. Effects of periosteal stripping on healing of segmental fractures in rats. *J. Orthop. Trauma* 10: 279–284. [Medline] [CrossRef]
31. Yonezawa, H., Yamada, S., Yanamoto, S., Yoshitomi, I., Kawasaki, G., and Umeda, M. 2012. Effect of polyglycolic acid sheets with fibrin glue (MCFP technique) on the healing of wounds after partial resection of the border of the tongue in rabbits: a preliminary study. *Br. J. Oral Maxillofac. Surg.* 50: 459–463. [Medline] [CrossRef]