Gelatin sheet incorporating basic fibroblast growth factor enhances sternal healing after harvesting bilateral internal thoracic arteries

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Objective: We previously reported that a gelatin sheet incorporating basic fibroblast growth factor accelerated sternal healing after bilateral internal thoracic artery removal in normal and diabetic rats. The aim of this study was to evaluate the effects of this therapeutic modality on sternal healing in a large-animal model before performing a clinical trial.

Methods: After median sternotomy and bilateral internal thoracic artery removal in a pedicled fashion, 14 beagle dogs received either a gelatin sheet incorporating basic fibroblast growth factor (100 μ g per sheet) on the posterior table of the sternum (FGF group, n = 7) or did not receive a gelatin sheet (control, n = 7). We compared sternal healing 4 weeks after surgical intervention between the groups.

Results: Scintigraphic images obtained by using technetium 99 methylene diphosphonate bone scanning were assessed visually, and the impulse rate was quantified 30 and 60 minutes after injection of technetium 99 methylene diphosphonate to evaluate the sternal perfusion. Sternal uptake was significantly increased in the FGF group (30 minutes: 221% $\pm$ 30% vs 180% $\pm$ 36%; 60 minutes: 267% $\pm$ 26% vs 197% $\pm$ 42%; $P < .01$). Apparent sternal dehiscence, as assessed radiographically, was observed only in the control animals. Histologically, complete healing of the sternum with marked angiogenesis was observed in the FGF group, whereas poor healing with limited angiogenesis was seen in the control animals. Both bone mineral content (134 $\pm$ 49 vs 52 $\pm$ 32 mg, $P < .01$) and bone mineral density (133 $\pm$ 53 vs 66 $\pm$ 32 mg/mm², $P < .05$) along the incision line of the sternum, as assessed by means of dual-energy x-ray absorptometry, were higher in the FGF group.

Conclusions: A gelatin sheet incorporating basic fibroblast growth factor enhances sternal perfusion and accelerates sternal bone healing in large animals.

The usefulness of bilateral internal thoracic arteries (BITAs) for myocardial revascularization has been shown in several clinical studies.¹⁻⁴ The use of BITAs improves long-term survival as a result of an attempt to avoid late saphenous vein occlusion and postoperative return of angina. However, BITA grafting has not been a common procedure at most cardiovascular institutions in spite of these apparent benefits. One of several reasons is that harvesting BITAs raises the potential for an increase in sternal wound complications after median sternotomy

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because BITAs are widely recognized as providing the major blood supply to the sternum. Although the incidence of deep sternal wound infection is low, the potential for increased mortality and morbidity is well documented.

Basic fibroblast growth factor (bFGF) has been well known as one of the potent mitogens, regulating proteins that induce the proliferation of a variety of cells, including epithelial and mesenchymal cells, and promoting the growth and regeneration of organs and tissues *in vivo*.⁵ Because bFGF in its free form had biologic activities insufficient to induce the expected results, tissue regeneration was not successful, except in some cases.^{6,7} Recently, we have developed a biodegradable hydrogel composed of acidic gelatin to enable bFGF to be released at the site of action for a sufficient time period by changing the water content of hydrogels.⁸ We previously reported that the topical use of a bFGF gelatin sheet applied to the sternum after the removal of BITAs accelerates sternal healing in normal and diabetic rats.^{9,10} The objective of the present study was to elucidate the effectiveness of this therapeutic modality for sternal healing in a large-animal model before performing a clinical trial.

Materials and Methods

Preparation of bFGF-incorporated Gelatin Hydrogel Sheets

Gelatin with an isoelectric point value of 4.9 was isolated from bovine bone collagen by means of an alkaline process using $\text{Ca}(\text{OH})_2$ (Nitta Gelatin Co, Osaka, Japan). Human recombinant bFGF with an isoelectric point value of 9.6 was supplied from Kaken Pharmaceutical Co (Tokyo, Japan). Gelatin hydrogel sheets were made as previously described.⁸ Sheets were freeze-dried, followed by impregnation with an aqueous solution containing 100 μg of bFGF, to obtain gelatin hydrogels incorporating bFGF. The prepared hydrogel sheets were rectangular (120×10 mm) and 0.7 mm thick. All experimental procedures were conducted under sterile conditions.

Animal Experiments

Fourteen male beagle dogs weighing between 10 and 15 kg were used in this study. Anesthesia was induced with xylazine (5 mg/kg), ketamine hydrochloride (12.5 mg/kg), and atropine (0.01 mg/kg) administered intramuscularly. The dogs were intubated in the supine position, and anesthesia was maintained with isoflurane (1%-1.5%). An intravenous antibiotic was administered before incision (cefazolin, 500 mg per dog). After a midline skin incision was made, the bilateral major pectoral muscles were divided from the junction of the sternum, and the intercostal muscles on both sides of the sternum were exposed. Median sternotomy was carefully performed with a rotating saw, leaving part of the sternum on both sides. Bleeding from the bone marrow was stopped with the use of bone wax (NESTOR, Nippon Shoji, Japan). The 14 dogs were randomly divided into 2 groups. The FGF group ($n = 7$) had the BITAs removed, and a gelatin hydrogel sheet that incorporated bFGF was placed on the posterior table of the sternum before the sternum was closed. The control group ($n = 7$) had the BITAs

removed, and the sternum was closed without the gelatin hydrogel sheet. BITAs were harvested in a pedicled fashion and were then ligated with 2-0 silk sutures near the takeoff point and at the distal bifurcation. When the gelatin hydrogel sheets with incorporated bFGF (100 μg per sheet) were placed in the animals, the internal thoracic artery (ITA) beds were also covered by the sheet from the inside of the chest wall, and the implant was stabilized with 5-0 polypropylene sutures on all sides to avoid movement behind the sternum. After positive end-expiratory pressure had been applied to fully inflate the lungs, the sternum was parasternally closed with 6 interrupted, braided polyester sutures. The muscle layer and the skin were carefully sutured with 2-0 nylon monofilaments. All the animal experiments were performed according to Kyoto University's institutional guidelines for animal experimentation.

Bone Scintigraphy

Bone scintigraphy was performed 4 weeks after the operation. Radioactive marked technetium-99m methylene diphosphonate ($^{99\text{m}}\text{Tc-MDP}$) was used as an indicator. $^{99\text{m}}\text{Tc-MDP}$ was supplied by Nihon Medi-Physics Co (Nishinomia, Japan). The dogs were anesthetized with xylazine (5 mg/kg) and ketamine hydrochloride (12.5 mg/kg), and the imaging was performed 30 and 60 minutes after injection of 291 MBq (approximately 0.79 mL) of $^{99\text{m}}\text{Tc-MDP}$ through the peripheral vein. All scintigraphic images were assessed visually by an investigator blinded to treatment assignments.

Computer-assisted image analysis was performed to quantify tracer uptake in the sternal wound. The sternum, as the region of interest (ROI), was divided into 3 parts (manubrium, corpus, and distal sternum). The posterior mediastinal cavity was the reference ROI because this region was not involved in the operation, and the count rate of this reference ROI was defined as 100%. The mean number of counts per pixel was calculated for each ROI and compared statistically.

Assessment of Bone Formation

All dogs were killed by means of intravenous administration of a lethal dose of sodium pentobarbital 4 weeks after the operation. The sternum was excised and fixed in 10-wt% formaldehyde solution in primary buffer solution for 4 days for assessment of the extent of bone regeneration. Bone regeneration of the sternum was assessed radiographically and by means of histologic examination. Soft-tissue (high-contrast) radiographs of the sternum were taken at 38 kV and 2 mA for 45 seconds by using an x-ray apparatus (type CMB; Koizumi X-Senkosha, Tokyo, Japan). Photographs of formalin-fixed bone specimens from different experimental groups were taken with the same type of x-ray film.

Bone regeneration of the sternum was also assessed by means of quantification of the bone mineral content (BMC) and bone mineral density (BMD) and by means of histologic examination. The BMD and BMC of each sternum were analyzed on the whole sternum and also on the 60×1 mm² ROI along the sternal incision line by dual-energy x-ray absorptometry with a bone mineral analyzer (Dichroma Scan 600; Aloka Co, Tokyo, Japan). The instrument was calibrated with a phantom of known mineral content. Each scan was performed at a speed of 20 mm/s, and the scanning length was 2 mm.

Figure 1. Sternal scintiscans with ^{99m}Tc -MDP 4 weeks after surgical intervention showing increased uptake in the FGF group (A) and reduced uptake in the control group (B).

Histologic Examinations for Angiogenesis and Sternal Regeneration

After assessment for bone formation, bone specimens were demineralized in 10-wt% ethylenediamine tetraacetic acid solution at 4°C for 3 days, embedded in paraffin, and sectioned at a thickness of 10 μm . Sections were obtained at the third, fourth, and fifth intercostal spaces of the sternum and stained with hematoxylin and eosin and azan.

The assessment of vascular density, including both arterioles (>25 and <100 μm in external diameter) and capillaries (<25 μm in external diameter), in preparations stained with hematoxylin and eosin was carried out in a 200 $\times$ field (0.442 mm^2 per unit area). Five fields were chosen randomly from the connective tissue around the sternum. Two pathologists blinded to treatment counted the number of vessels per unit area, as described previously.¹⁰

Statistical Analysis

Experimental results are expressed as the mean $\pm$ SD. Statistical analysis comparing 2 groups was performed with the Wilcoxon rank sum test for means or the Fisher exact probability test for categorical variables.

Results

Radionuclide Imaging

Scintigraphic images were evaluated visually and quantitatively. Blinded comparison between the 2 groups revealed higher homogenous tracer uptake in the sternum in the FGF group (Figure 1, A) compared with that in the control group (Figure 1, B). The quantitative analysis of tracer uptake is summarized in Figure 2. Sternal uptake in the FGF group was significantly greater than that in the control animals at both 30 and 60 minutes after ^{99m}Tc -MDP injection (30 minutes: 221% $\pm$ 30% for the FGF group vs 180% $\pm$ 36% for the control group; 60 minutes: 267% $\pm$ 26% for the FGF group vs 197% $\pm$ 42% for the control group; $P < .01$).

Histologic analysis suggested an increase of sternal perfusion in the FGF group. Both capillaries and arterioles in

Figure 2. Quantitative analysis of sternal uptake 30 and 60 minutes after the injection of ^{99m}Tc -MDP 4 weeks after surgical treatment of the FGF and control groups.

the connective tissue around the regenerated sternum were more evident in the FGF group than in the control group (Figure 3). Figure 4 shows the number of arterioles and capillaries per unit area around the sternum 4 weeks after surgical intervention in both groups. The number of vessels per unit area around the sternum increased to a greater extent in the FGF group than in the control group (40.0 $\pm$ 3.5 vessels per unit area for the FGF group vs 18.1 $\pm$ 5.6 vessels per unit area for the control group; $P < .01$).

Assessment of Bone Formation

High-contrast radiographic images of the sternum 4 weeks after surgical treatment are shown in Figure 5. Dehiscence of the separated original sternum was observed in 2 dogs in the control group. In contrast, all dogs in the FGF group had sternal union and almost complete bone regeneration (rate

Figure 3. Micrographs stained with hematoxylin and eosin showing new blood vessel formation in connective tissue around the sternum 4 weeks after surgical treatment of the FGF (A) and control (B) groups. Increased numbers of capillaries and arterioles are indicated (arrowheads). NB, New bone.

Figure 4. Quantitative analysis of the number of vessels in connective tissue around the sternum 4 week after surgical treatment of the FGF and control groups.

of sternal dehiscence = 0.0% vs 71.3%; $P = .02$). In all dogs with sternal dehiscence in the control group, none had evidence of macroscopic abscess in the anterior mediastinum. There were no macroscopic findings indicating that the implanted gelatin sheets remained 4 weeks after surgical intervention.

Figure 6, A and B, shows histologic sections of the sternum 4 weeks after surgical intervention. Histologic examination revealed evidence of a little endochondrial ossification around the original sternum in both groups. However, complete bone regeneration along the incision of the sternum was observed only in the FGF group (Figure 6, C). In contrast, histologic analysis of the control group revealed invasion of fibrous tissue and inflammatory cells into the separated sternal space rather than sternal regeneration (Figure 6, D).

The BMC (1082 ± 413 vs 749 ± 216 mg) and BMD (107 ± 22 vs 84 ± 15 mg/mm²) of the whole sternum, as

assessed by means of dual-energy x-ray absorptometry, did not indicate a significant difference between the FGF and control groups, as shown in Figure 7. However, the BMC along the incision line of the sternum in the FGF group was significantly higher than that in the control group (134 ± 49 vs 52 ± 32 mg, $P < .01$). Also, the BMD in the FGF group showed a significant increase compared with that in the control group (133 ± 53 vs 66 ± 32 mg/mm², $P < .05$) because the BMD was calculated at the same 60×1 mm² ROI in all samples.

Discussion

Bone scintigraphy with ^{99m}Tc-MDP is commonly used in the diagnosis of bone disease. ^{99m}Tc-MDP is a radionuclide with excellent imaging characteristics, including pure gamma emission with a single low-energy gamma peak, a short half-life (6 hours), and a reasonable cost per dose.¹¹ Although many characteristics of the mechanism of accumulation to bone have not been clarified, it is generally assumed that ^{99m}Tc-MDP accumulates at the sites of active bone metabolism. Several authors have already evaluated the sternal perfusion after harvesting bilateral or unilateral ITAs using scintigraphic techniques.^{12,13} Using bone scans, Cohen and colleagues¹⁴ have shown that a pedicled left ITA graft to the left anterior descending artery reduces blood flow to the left side of the sternum during the acute post-operative period. In this study our results reveal higher uptake in the FGF group compared with that in the control group both at 30 and 60 minutes after the injection of ^{99m}Tc-MDP. Moreover, histologic sections in the FGF group disclose marked angiogenesis around the regenerated sternum and active bone metabolism along the incision line of the sternum. Also, there is little possibility that the increased uptake in the FGF group was due to increased inflammation caused by the delivery system of bFGF. We

Figure 5. Radiograph showing sternal bone regeneration 4 weeks after surgical treatment in dogs. A, Almost complete sternal regeneration was seen in the FGF group. B, Obvious sternal dehiscence was observed in the control group (arrowheads).

could not find the unabsorbable gelatin sheet 4 weeks after the operation in the FGF group, and the histologic assessment in the FGF group did not detect more inflammatory cells around the regenerated sternum compared with those seen in the control group. These findings suggest that the delivery system has a minimum inflammatory effect at the scintigraphic assessment. We believe that the higher uptake of ^{99m}Tc -MDP demonstrates active sternal bone metabolism as a result of an increase of sternal perfusion because the quantitative analysis of the vascular density around the sternum also supported this speculation.

Recently, modifications in the technique of ITA harvesting, such as skeletonization of the ITA, have been suggested as a means of preserving the collateral blood supply to the sternum after ITA mobilization.^{15,16} This concept has also been supported in some anatomic studies on sternal blood supply.¹⁷⁻¹⁹ Pietrasik and colleagues²⁰ have reported that most ITA branches can originate as a common trunk, and potential anastomoses can occur across these joint branches after ITA mobilization. The blood flow to the sternum might be preserved by division of the ITA branches close to the ITA itself after careful harvesting of the common trunk. However, angiographic study in human subjects²¹ has revealed numerous variations in ITA branching patterns. As a result, even careful skeletonization can destroy collaterals from the lateral chest wall to the sternum (eg, solitary branches). Thus, skeletonization might be useful for some patients but not for all patients who need or would potentially benefit from BITA grafts for coronary revascularization. On the contrary, this trial with the gelatin hydrogel sheet incorporating bFGF is a novel regenerative approach

to the devascularized sternum after BITA harvesting. Our data in this study reveal that a gelatin hydrogel sheet incorporating bFGF improves sternal healing after harvesting BITAs, even in a pedicled fashion that might cause severe sternal ischemia. Moreover, although diabetic patients are considered at increased risk for sternal wound complications and thus have been largely excluded from receiving BITA grafting,^{22,23} this method improved sternal healing after BITA removal, even in diabetic animals.¹⁰ It is very likely that this method can potentially extend the use of BITAs in coronary bypass surgery.

Because bFGF functions as a potent mitogen for mesenchymal cells, it has the potential to be a key factor for tissue engineering of the sternum, inducing not only neovascularization but also osteogenesis. This osteogenic effect of bFGF consists of acceleration of callus remodeling both by means of osteoblastic callus formation and osteoclastic callus resorption.²⁴ In this study we did not evaluate the group that had the gelatin sheets without incorporating bFGF because the empty gelatin had no effect in enhancing bone formation in our previous investigation using skull-defect models in rabbits.⁸ Our histologic results also confirm that the gelatin hydrogels incorporating bFGF accelerate sternal regeneration after median sternotomy, even in a large animal. We have previously measured the BMD and BMC in a small-animal model as an indicator of qualitative and quantitative analysis, respectively. Both the BMD and BMC measurements in the whole sternum showed no significant differences between the 2 groups in this study, despite those in the FGF group along the incision line of the sternum being significantly increased compared with those in the

Figure 6. Histologic cross-sections of azan-stained sternum were obtained 4 weeks after surgical treatment. Whole sternal feature in the FGF (A) or control (B) groups was shown at a low magnification (2 $\times$). Regenerated sternal bone was observed along the incision line of the sternum only in the FGF group (C). Fibrous tissue instead of regenerated bone invaded the space between the separated original sternum (D). OS, Original sternum; NB, new bone.

control group. This might be caused by the much smaller area of regenerated sternum compared with the nonregenerated sternum in a large animal. Also, the FGF group was associated with a significant trend toward decreased sternal dehiscence in spite of no mechanical care of the sternum postoperatively. These findings suggest that the regenerated sternum induced by a gelatin sheet incorporating bFGF might be strong and stable enough to be helpful clinically.

There are several limitations in the present study. First, the sternal feature, even in a large animal, is not the same as that in a human subject. It is undeniable that structural differences might influence sternal healing induced by the bFGF sheet. However, a pilot study with cynomolgus monkeys showed that the use of bFGF sheets accelerated sternal regeneration after BITA mobilization, although there was some (although fewer) structural differences from a human subject. Therefore we believe that our method can enhance

sternal healing, even in human subjects. Second, hematoxylin-and-eosin staining might not be optimal for the assessment of vascular density. However, it is meaningful to evaluate the vascular density by using hematoxylin-and-eosin staining as a blood supply to the sternum because the results would reflect the number of large vessels rather than capillaries around the regenerated sternum. The final potential limitation concerns the systemic effects of bFGF. Specifically, the angiogenic potential of bFGF might cause a clinical worsening of symptoms in patients with diabetic retinopathy and neoplasm. However, bFGF in its free form (ie, a higher serum level of bFGF) has been commercially available as a treatment for skin ulcers in Japan, with no reported problems. In addition, clinical trials of bFGF for the treatment of myocardial ischemia have revealed no complications of exogenously administered protein.²⁵

Figure 7. BMC (left) and BMD (right) were analyzed on the whole sternum and along the sternal median incision line (60 × 1 mm² ROI) by means of dual-energy x-ray absorptometry after surgical treatment of the FGF and control groups.

In conclusion, the gelatin sheet incorporating bFGF enhances sternal perfusion and accelerates sternal bone healing, despite pedicled BITA removal after median sternotomy, even in large animals, especially by inducing neovascularization and osteogenesis. These results warrant further investigation in a clinical trial. We are in the process of making an application for this clinical trial, which has been submitted to the ethical committee at Kyoto University, Japan.

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