Case Report

Coverage of Free Flap Vascular Pedicles by Basic Fibroblast Growth Factor-impregnated Collagen-Gelatin Sponge Without Skin Graft

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ABSTRACT

In a 49-year-old man, a free flap was grafted to cover a tissue defect after surgery for frontal osteomyelitis. On the following day, due to venous thrombosis, the patient underwent removal of the venous thrombus and vascular re-anastomosis with a vein graft. A basic fibroblast growth factor-impregnated collagen-gelatin sponge (bFGF-CGS) was used to close the wound without compression of the vascular pedicles. Postoperatively, the free flap survived without recurrence of venous thrombosis, and the bFGF-CGS graft site was completely epithelialized without additional skin grafting. The grafted bFGF-CGS slowly released basic fibroblast growth factor, which in turn continuously promoted the proliferation of fibroblasts, angiogenesis, and epithelialization. Furthermore, bFGF-CGS is more durable because of its double-layered structure, and compression fixation is not required after grafting. The bFGF-CGS appears to be useful for the coverage of vascular anastomotic sites and vascular pedicles after free flap grafting, which requires strict management. Therefore, bFGF-CGS is an excellent material for regenerative medicine. We report its usefulness with regard to our first case, in which it was used to cover free flap vascular pedicles.

Key words : artificial dermis, basic fibroblast growth factor, drug delivery system, free flap, venous thrombosis

Introduction

Free tissue flap grafting has been established as a reconstructive surgical procedure for tissue defects due to malignant tumor surgery, trauma, and so on. Free flap grafting necessitates anastomosis of the recipient and donor tissue vessels. The survival rate of grafted tissue flaps has been reported to be approximately 95%. Additionally, microvascular complications have been reported to occur in 2%–5% of cases. The most serious postoperative complication has been observed to be venous thrombosis. At the sites of vascular anastomoses or vascular pedicle grafting, the wound is usually closed by a simple suture of the surrounding normal skin or covered with an extended skin paddle of a free flap. However, simple sutures may be difficult, depending on the texture or tension of the skin around the wound at the graft bed and the amount of grafted tissue. In such cases, closure by forced suture causes tension or compression, which increases the risk of postoperative complications, such as venous insufficiency, flap congestion, and venous thrombosis. Thus, vascular grafts may be covered by skin grafting, artificial dermis grafting, and so on.

Notably, upon the formation of venous thrombi at anastomotic sites, reoperation is necessary to remove thrombi and repeat vascular anastomosis for the salvage of free flaps. The salvage rate of free flaps is reported to decrease as the frequency of reoperations increases. After reoperation, venous anastomotic sites and flap vascular pedicles should be carefully monitored and not be compressed to prevent the recurrence of venous thrombosis.

In contrast, grafting of the artificial dermis is recognized as a standard treatment for wound treatment. Artificial dermis is used as a material for reconstructive surgical procedures for full-thickness skin defects and is reported to be a useful biomaterial. In 2013, Morimoto et al. developed a novel hybrid artificial dermis equipped with a basic fibroblast growth factor (bFGF) drug delivery system and conducted a clinical
trial on chronic ulcers\(^{12}\). The bFGF-impregnated collagen gelatin sponge (bFGF-CGS) was prepared by adding 10% alkali-treated gelatin to the conventional artificial dermis. This alkali-treated gelatin binds to the positively charged bFGF. As the gelatin is absorbed into the body, bFGF is gradually released on the wound surface over a period of 3 weeks\(^{13}\). In Japan, bFGF formulations have already been clinically used as effective wound healing agents for skin ulcers\(^{14,15}\). The bFGF-CGS is expected to increase the therapeutic effects of bFGF, such as promoting granulation, angiogenesis, and epithelialization, compared to conventional artificial dermis.

We used bFGF-CGS to cover the vascular pedicles during the reoperation of a patient with venous thrombosis after free flap grafting. Here, we report the usefulness of the bFGF-CGS for the first case of covering the free flap pedicles at our institution.

**Clinical case**

A 49-year-old man developed right blepharospasm several years earlier. He subsequently noted facial myokymia. In the Department of Neurosurgery at our hospital, he was diagnosed with frontal arteriovenous malformation and underwent craniotomy for extirpation of the malformation. Two months after the surgery, he developed frontal osteomyelitis, which required removal of the frontal bone. The surgery was jointly planned by the department of neurosurgery and the department of plastic and reconstructive surgery for the treatment of tissue defects resulting from the resection of bone and surrounding tissues.

During surgery, the Department of Neurosurgery performed craniotomy at the previous surgical scar, removal of the frontal bone affected by osteomyelitis and the titanium bone fixation plate, and debridement of the surrounding infected tissues. Subsequently, our department of plastic surgery performed grafting of a latissimus dorsi musculocutaneous free flap that was harvested from the right back for the skin and soft tissue defects caused by the preceding procedures. A large flap including the latissimus dorsi muscle beyond the skin paddle (21 × 7 cm) was raised and dissected with the thoracodorsal artery and vein up to the bifurcation as vascular pedicles. The superficial temporal artery and vein were selected as recipient vessels. The superficial temporal artery and vein were secured using a right pre-auricular skin incision. The flap was fixed to the head defect. Then, end-end anastomosis was performed with 9-0 nylon separately for the arteries and veins under a microscope. The site of vascular pedicle grafting and vascular anastomosis was closed by simple closure of the pre-auricular recipient skin (Fig. 1). Although the blood flow in the flap was favorable immediately after surgery, congestion occurred in the flap on postoperative day (POD) 1, presumably because of tension and compression of the vascular pedicles due to simple suture (Fig. 2). Thus, a reoperation was performed.

In the operating room, the wound at the vascular anastomotic site was opened, and microscopic examination revealed anastomotic venous thrombosis. The anastomosed vein was

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**Fig. 1.** Immediately after surgery.
A latissimus dorsi musculocutaneous free flap was grafted onto the forehead. The superficial temporal artery and vein in the right pre-auricular area were anastomosed with the thoracodorsal artery and vein, which were the blood vessels of the flap. The surrounding skin was sutured directly to close the wound.

**Fig. 2.** The grafted flap on postoperative day 1.
The color of the skin paddle indicated congestion.
resected, and the thrombus was removed. Although venous anastomosis was attempted after resection of the blood vessel with thrombus formation, direct anastomosis was cumbersome. Thus, vein grafting was performed using the right cephalic vein as a donor to reconstruct venous outflow (Fig. 3). Venous reperfusion and improvement of congestion in the flap were confirmed after vascular re-anastomosis, and the wound was closed. In the pre-auricular area where the vein was grafted, direct closure of the skin was difficult because of the excessive tissue resulting from vein grafting. Thus, the vascular pedicles were covered with bFGF-CGS (Fig. 4).

bFGF-CGS was prepared according to the method reported by Matsumine et al.\textsuperscript{16} Size S (82 × 60 mm) of artificial dermis containing negatively charged gelatin (Pelvac Gplus mesh-reinforced type; Gunze Japan) was arranged with its collagen side upward. On this side, 500 μg of positively charged bFGF (trafermin) spray (Fiblast; Kaken Japan) was instilled to impregnate the artificial dermis for 10 min. The concentration of bFGF administered was approximately 10 μg/cm\textsuperscript{2}. After bFGF was added, the artificial dermis was cut to an appropriate size, applied to the defect, and fixed with nylon thread. As for the thickness, the artificial dermis consisted of an upper silicone sheet (0.12 mm in thickness) and a lower collagen sponge with alkali-treated gelatin (3 mm in thickness). The bFGF-CGS was adjusted to the size of the tissue defect (10 × 2 cm) and roughly sutured with nylon thread for fixation; ointment was applied to the bFGF-CGS. The bFGF-CGS was subsequently gently covered with gauze without compression.

After surgery, blood flow was monitored using a Doppler stethoscope every 2 h. Blood flow was confirmed by directly placing the stethoscope on the silicone sheet of the bFGF-CGS. The silicone sheet was removed on POD 7, and the ointment treatment was continued. On POD 14, the wound was well granulated and contracted (Fig. 5). On POD 28, the wound was completely epithelialized (Fig. 6). After the surgery, the grafted flap completely survived without recurrence of anastomotic thrombosis or complications, such as flap necrosis. Second-stage cranioplasty is scheduled to be performed at the Department of Neurosurgery.

This case study was approved by the Ethics Committee of the Tokyo Women’s Medical University. The patient provided written informed consent to participate in the study.

Discussion

In the present study, bFGF-CGS was used to cover the vascular pedicles after free flap grafting and to close the wound. This allowed us to avoid compression of the vascular anastomotic site, which caused anastomotic thrombosis. Furthermore, the wound epithelialized without two-stage skin grafting. We consider that the usefulness of bFGF-CGS is attributable to the following three reasons.

First, the promoting effects of bFGF on the proliferation of fibroblasts\textsuperscript{17} and angiogenesis\textsuperscript{18} allow early regeneration of firm dermis-like tissues. For the coverage of flap vascular
pedicles, sufficiently thick tissues are necessary to maintain stable blood flow and to protect the pedicles from external factors, such as trauma. The grafting site is generally closed by simple closure of the skin of the graft bed or covered with a part of the skin paddle of the grafted tissues. When simple closure is impossible, skin grafts or an artificial dermis may be used for coverage. As bFGF-CGS can form thick dermis-like tissues, it is expected to be effective in protecting vascular pedicles.

Second, bFGF-CGS alone was effective for epithelialization. bFGF promotes keratinocyte proliferation and epithelialization. When skin grafting is selected for coverage of the flap vascular pedicles, compression fixation of the skin grafting site is necessary. This may cause flap congestion. In contrast, grafting of bFGF-CGS does not require compression fixation, which is necessary for skin grafting. Therefore, the risk of congestion can be avoided. Matsumine et al. reported cases of fingertip amputation in which the bFGF-CGS was used for tissue defects and the wounds were successfully closed without two-stage skin grafting. In our patient, epithelialization was also achieved without two-stage skin grafting.

Third, the CGS has a double-layered structure. Pelnac Gplus consists of a collagen layer and a silicone film. As the silicone film ensures the durability and form of Pelnac Gplus, it can be cut into an appropriate size and reshaped. Levin et al. reported that the acellular dermal matrix is easy to reshape and use. Thus, CGS can be used regardless of the size or shape of the skin defects. As in our case, the use of CGS prevented compression due to closure of the skin and allowed for the avoidance of procedures invasive to the donor site, such as skin grafting. In addition, a Doppler stethoscope and other monitoring devices can be used on the silicone film without direct contact with the collagen layer. CGS is very useful for postoperative monitoring of blood flow in flaps.

This study has several limitations. Although our procedure using an already commercially available device can be applied immediately, the grafting of artificial dermis impregnated with bFGF is not currently covered by the National Health Insurance in Japan. The application of our procedure requires approval from ethics committees. In addition, epithelialization takes a few weeks longer for our procedure than for wound closure by skin grafting. A slightly longer duration of ointment treatment is a disadvantage. The maximum size of the covering bFGF-CGS is approximately 100 cm², depending on the daily dose limit of bFGF. According to the present case, a width of up to 2 cm can be closed in a one-stage operation and subsequent epithelialization without additional skin grafting. In addition, one of the expected complications is hematoma, which can compress the vascular pedicles. To avoid hematoma formation, it is advisable to exclude hemorrhagic patients, and patients on drugs that impair hemostasis due to the increased risk of bleeding.

**Conclusion**

We used the bFGF-CGS to cover the free flap vascular pedicles after vein resection with the thrombus. The use of bFGF-CGS allowed us to avoid compression of the vascular pedicles and achieve complete epithelialization without
additional surgery. The bFGF-CGS is suggested to be useful because it regenerates firm dermis-like tissues by slowly releasing bFGF and promoting epithelialization.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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