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Letter to the editor

# Two-stage skin grafting using a basic fibroblast growth factor-impregnated artificial dermis

*Keywords:*
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A B S T R A C T

For traditional artificial dermises, a waiting period of approximately three weeks is required after the first implantation before they are adequately vascularized. The objective of this retrospective case series was to investigate whether full-thickness skin defects, requiring surgical reconstruction, could be successfully treated by implantation of a basic fibroblast growth factor (bFGF)-impregnated artificial dermis and secondary skin grafting with a shorter waiting period. Between January 2019 and January 2021, 19 skin defects in 14 patients (7 male and 7 female) were treated with two-stage skin grafting using bFGF-impregnated collagen-gelatin sponge (CGS). All of them were included in this case series, and the waiting period for skin grafting, success rate of skin grafting, infection during the waiting period, and scar quality 6–12 months postoperatively were retrospectively investigated. As a result, all skin grafting surgeries were successfully performed with a waiting period of 13.3 ± 4.3 days. Infection during the waiting period was observed in three lesions (15.8%); however, all infections were controllable. Postoperative scar quality was acceptable (Vancouver Scar Scale score range, 1–8). In conclusion, compared to traditional artificial dermises, bFGF-impregnated CGSs have the potential to shorten the waiting period without decreasing the success rate of skin grafting. Further studies are required to confirm this finding.



## 1. Introduction

Since the basic design principles and performance of an artificial dermis were first reported by Yannas et al. [1] in 1980, two-stage skin grafting using an artificial dermis has been indicated for large, full-thickness skin defects resulting from burns [2], injuries [3], and surgical resection of skin tumors [4]. Currently available artificial dermises, such as Pelnac®, Integra®, and Terudermis®, are bilayered and composed of an inner biodegradable template of collagen and an outer silicone sheet that prevents collagen desiccation. A few weeks post-implantation, the biodegradable layer is converted into regenerated autologous dermis-like tissue, providing a good wound bed for secondary thin, split-thickness skin grafting [5]. The use of an artificial dermis has been reported to improve the success rate of skin grafting and reduce postoperative contracture [5,6]. However, a waiting time is required for well-vascularized tissue to regenerate in the biodegradable layer, and this is a challenge. The waiting time causes a prolonged burden on patients and increases the incidence of wound infection [7,8]. Promoting wound healing and reducing the length of the waiting time might reduce not only the burden on patients, but also the risk of infection and, as a result, improve the success rate of secondary skin grafting.

To address these issues, we previously developed a novel artificial dermis, composed of 90 wt% porcine tendon atelocollagen and 10 wt% porcine dermal gelatin (collagen/gelatin sponge, CGS), which is capable of sustained release of basic fibroblast growth factor (bFGF) for more than 10 days [9]. Basic fibroblast growth factor was first isolated by Gospodarowicz [10], and it is known to bind to and activate FGF receptors and regulate cell proliferation, migration, differentiation, and angiogenesis [11–13]. As expected, bFGF-impregnated CGS accelerated wound healing in animal models [9,14]. The safety and efficacy of CGS impregnated with bFGF was confirmed in a first clinical trial on the treatment of chronic ulcers (2010–2011) [15], and in 2018, CGS was approved in the Japanese clinical market as Pelnac Gplus® (Gunze Co., Ltd., Ayabe, Japan), a modified version of the conventional artificial dermis, Pelnac® (Gunze). However, clinical data on the treatment of large, full-thickness skin defects using bFGF-impregnated CGS and secondary skin grafting are lacking. The objective of this study was to investigate whether full-thickness skin defects requiring surgical reconstruction could be successfully treated by implantation of bFGF-impregnated CGS and secondary skin grafting for a short duration.

*Abbreviations:* bFGF, basic fibroblast growth factor; CGS, collagen-gelatin sponge; GCMN, giant congenital melanocytic nevus; MRSA, methicillin-resistant *Staphylococcus aureus*; VSS, Vancouver Scar Scale.

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**Table 1**
Summary of cases.

| Case no. | Sex | Age (Years) | Disease | Location | Defect size (%) | Infection | Waiting time (Days) | Skin grafting | VSS score | Follow up (Months) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 60 | Burns | right upper arm | 4.5 | N | 14 | S | 7 | 9 |
| 2 | M | 4 | GCMN | back | 10.0 | N | 11 | S | 8 | 12 |
| | | 5 | GCMN | left hip | 2.5 | N | 11 | S | 8 | 11 |
| | | 5 | GCMN | right hip | 2.5 | N | 14 | S | 4 | 6 |
| | | 6 | GCMN | left abdomen to lateral abdomen | 6.5 | N | 14 | S | 4 | 7 |
| 3 | F | 3 | GCMN | left lower leg | 2.75 | O(PA) | 14 | S | 5 | 10 |
| 4 | F | 5 | Burns | right precordium | 1.0 | N | 14 | S | 7 | 9 |
| 5 | M | 2 | GCMN | right upper arm | 1.5 | N | 14 | S | 7 | 12 |
| 6 | M | 28 | Traumatic skin defect | left ankle joint | 1.0 | N | 17 | S | 8 | 7 |
| 7 | M | 46 | Arterioverous fistula | head | 2.0 | N | 7 | S | 1 | 12 |
| 8 | F | 60 | cellulitis | left ankle | 3.0 | N | 21 | S | 8 | 7 |
| 9 | M | 83 | Intractable ulcer | left lower leg | 2.0 | N | 8 | S | 8 | 9 |
| 10 | F | 79 | Burns | left lower leg | 1.0 | N | 11 | S | 6 | 10 |
| | | 79 | Burns | right lower leg | 1.0 | N | 6 | S | 6 | 10 |
| | | 79 | Burns | right & left foot | 1.0 | N | 9 | S | 3 | 6 |
| 11 | F | 62 | Intractable ulcer | right & left foot | 0.5 | O (MRSA) | 20 | S | 5 | 6 |
| 12 | F | 0 | GCMN | left upper leg | 2.0 | O (MRSA) | 20 | S | 3 | 12 |
| 13 | M | 47 | Necrotizing fasciitis | left lower leg | 2.0 | N | 11 | S | 6 | 9 |
| 14 | F | 1 | GCMN | back to hip | 5.0 | N | 16 | S | 6 | 6 |

M, male; F, female; GCMN, giant congenital melanocytic nevus; O, occurred; N, did not occur; PA, *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; S, success; VSS, Vancouver Scar Scale.

## 2. Case reports

### 2.1. Patients

This case series was reviewed and approved by the institutional review board of Kyoto University Hospital (permission number R2943). The requirement for written informed consent was waived by the board, and we applied the opt-out method to obtain consent. This work was carried out in accordance with the Declaration of Helsinki. Between January 2019 and January 2021, consecutive patients with large, full-thickness skin defects, who underwent implantation of a bFGF-impregnated CGS followed by secondary skin grafting at the Department of Plastic and Reconstructive Surgery, Kyoto University Hospital, were included. Nineteen lesions from 14 patients (7 male and 7 female) were treated during the study period. The patients' mean age was 35.8 ± 32.5 (0–83 years). The primary diseases were giant congenital melanocytic nevus (GCMN) (n = 5), burns (n = 3), chronic ulcers (n = 2), necrotizing fasciitis (n = 1), traumatic skin defect (n = 1), cellulitis (n = 1), and facial arteriovenous fistula (n = 1).

### 2.2. Surgical procedure and outcomes

In the first surgery, resection of skin/soft tissue tumors or debridement of chronic ulcers was performed, resulting in full-thickness skin defects without necrotic tissue. Before the implantation of Pelnac Gplus®, recombinant human bFGF (Fibrast® Spray; Kaken Pharmaceutical, Tokyo, Japan) was dissolved in sterile distilled water to prepare 100 μg/mL bFGF solution. The bFGF solution was applied using a 5 mL syringe to the collagen side of Pelnac Gplus® and incubated for 10 min at room temperature for the impregnation of bFGF. The impregnation concentration was about 10 μg/cm$^2$. When the skin defect was large, the concentration was decreased to ensure that the total bFGF dose did not exceed 1000 μg, according to the Japanese guidelines for Fibrast® Spray. The bFGF-impregnated Pelnac Gplus® was sutured to the skin defect and covered with gauze. Prophylactic antimicrobials were administered for 1–3 days postoperatively. After the initial wound check on day 1, the wound was washed and disinfected as needed to keep it clean, depending on the exudate status. In case of suspected infection, the silicone sheet of Pelnac Gplus® was removed, and therapeutic antimicrobials were administered. After good granulation tissue was formed under the silicone sheet, the patient underwent a secondary split-thickness skin grafting. All patients underwent both first and second surgeries during their first hospitalization.

For patients with a postoperative duration of at least 6 months, the following information was retrospectively obtained from their electronic medical records and gross photographs: age, sex, primary disease and affected site, size of skin defect, waiting time for secondary skin grafting, incidence of infection during the waiting period, success or failure of skin grafting, and postoperative contractures. The size of the skin defect was estimated using the Lund and Browder chart [16]. Wound infection was defined as the presence of signs of infection (redness, heat, pain, purulent exudate) at the wound site, systemic symptoms (fever and elevated inflammatory response in blood tests), and positive wound culture [17–19]. If more than 90% of the area epithelialized 10–14 days after skin grafting without signs of infection, skin grafting was judged to be successful. Postoperative contractures were evaluated using the Vancouver Scar Scale (VSS) by analyzing photographs taken 6–12 months postoperatively. The VSS score was determined based on four parameters: vascular distribution (0–3), pigmentation (0–2), flexibility (0–5), and scar height (0–3), with 0 indicating normal skin [20–22]. Continuous variables are presented as mean ± standard deviation.

As a result, skin grafting was successful for all lesions and the waiting time for skin grafting was 13.3 ± 4.3 (6–21) days (see Table 1). During this period, three of the 19 treated lesions (15.8%) were infected. The causative organisms were methicillin-resistant *Staphylococcus aureus* (MRSA) in two cases and *Pseudomonas aeruginosa* in one case. Of the three infections, two improved with removal of the silicone sheet, washing, and prophylactic administration of antibiotics, followed by good granulation tissue

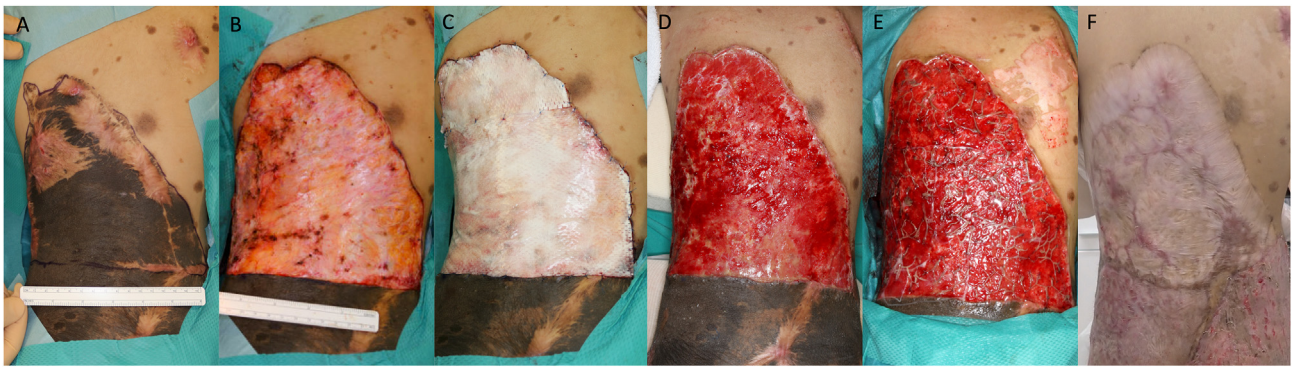


**Fig. 1.** Case 2, 4-year-old boy with dorsal giant congenital melanocytic nevus (A) Preoperative gross appearance (B) After tumor excision (C) After the first surgery (D) Dermis-like tissue observed on day 11 after the initial surgery (E) Split-thickness 6:1 meshed skin grafts of 0.3 mm thickness and cultured epithelial autografts applied to the wound (F) Twelve months after skin grafting surgery.

formation. In contrast, bFGF-impregnated Pelnac Gplus® was reapplied 10 days after the first surgery, and after 10 days, skin grafting was successfully performed. In all cases, the VSS was analyzed from photographs taken 8.95 ± 2.19 months after skin grafting, and the score was 6.07 ± 1.99, ranging from 1 to 8 points.

### 2.3. Representative cases

#### 2.3.1. Case 2

This was a 4-year-old male patient with a GCMN covering his back, buttocks, and flanks (Fig. 1A). During the first surgery, the dorsal lesion was excised with its subcutaneous tissue to ensure complete removal of its skin appendages (Figs. 1B) and 3.47 μg/cm$^2$ of bFGF-impregnated Pelnac Gplus® was implanted into the wound (Fig. 1C), which was secured a negative pressure wound therapy system. Prophylactic antimicrobials were administered for 3 days postoperatively. There was no wound infection during the postoperative period. After eleven days, good granulation tissue was formed (Fig. 1D), and 6:1 meshed skin grafts of 0.3 mm thickness and cultured epithelial autografts (JACE®, Japan Tissue Engineering Co., Ltd., Aichi, Japan) were applied to the wound (Fig. 1E). Twelve months postoperatively, there was no erosion formation in the wound, and the VSS score was 8 points (Fig. 1F). The remaining lesions were treated similarly.

#### 2.3.2. Case 5

This was a 2-year-old male patient. A right upper arm GCMN (Fig. 2A) was excised with its subcutaneous tissue to ensure complete removal of its skin appendages (Figs. 2B) and 5.01 μg/cm$^2$ of bFGF-impregnated Pelnac Gplus® was implanted (Fig. 2C), which was secured with gauze dressing. Prophylactic antimicrobials were administered for 3 days postoperatively. There was no wound infection during the postoperative period. After a waiting period of 14 days (Fig. 2D), sheet skin grafts of 0.3 mm thickness were applied to the wound (Fig. 2E). Twelve months postoperatively, there was no erosion formation in the wound, and the VSS score was 7 points (Fig. 2F). The ranges of motion of the shoulder and elbow joints were not impaired.

#### 2.3.3. Case 12

This was an 11-month-old female patient. A GCMN on her left thigh (Fig. 3A) was excised with its subcutaneous tissue (Figs. 3B) and 10.2 μg/cm$^2$ of bFGF-impregnated Pelnac Gplus® was implanted (Fig. 3C), which was secured with gauze dressing. Prophylactic antimicrobials were administered for 1 days postoperatively. The patient had a fever of 39.1 °C on day 8. Large amounts of leachate and MRSA were detected in the wound culture. After treatment with an oil-based ointment (Isodine Sugar Paste Ointment; Shionogi Co, Ltd., Tokyo, Japan) and vancomycin for 5 days, the patient's fever began to subside on postoperative day 13, and the amount of leachate decreased. After a waiting period of 20 days (Fig. 3D), good granulation was observed, and 3:1 meshed skin grafts of 0.3 mm thickness and cultured epithelial autografts were applied (Fig. 3E). Two weeks after surgery, the wound epithelialized well. Twelve months postoperatively, there was no erosion formation in the wound, and the VSS score was 3 points (Fig. 3F).

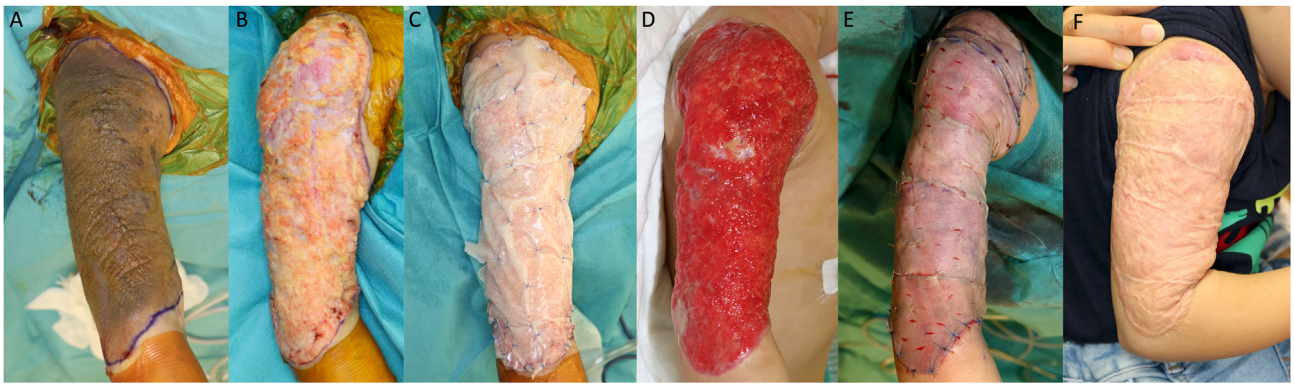


**Fig. 2.** Case 5, 2-year-old boy with giant congenital melanocytic nevus on the upper arm (A) Preoperative gross appearance (B) After tumor excision (C) After the first surgery (D) Dermis-like tissue observed on day 14 after the initial surgery (E) Sheet skin grafts of 0.3 mm thickness applied to the wound (F) Twelve months after skin grafting surgery.

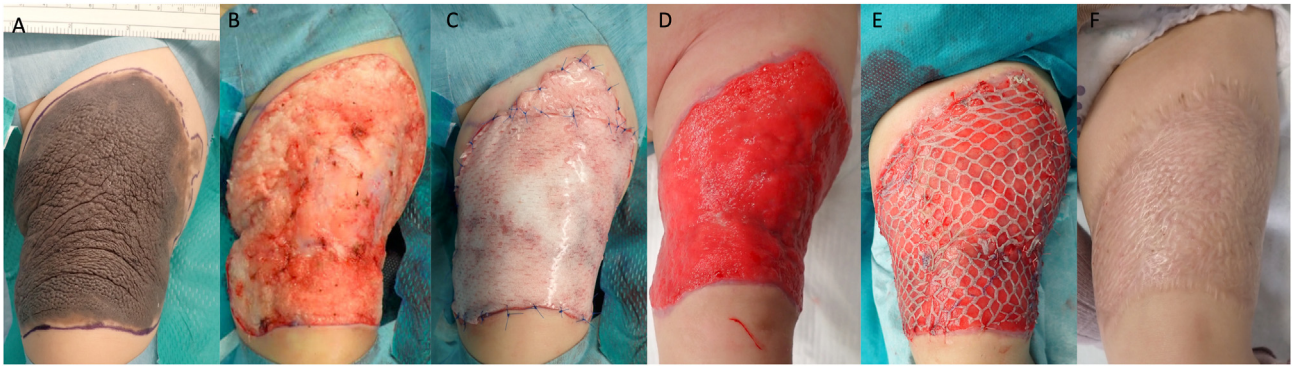


**Fig. 3.** Case 12, 11-month-old girl with congenital Giant Melanocytic Nevus on the left thigh (A) Preoperative gross appearance (B) After tumor excision (C) After the first surgery (D) Dermis-like tissue observed on day 20 after the initial surgery (E) Split-thickness 3:1 meshed skin grafts of 0.3 mm thickness and cultured epithelial autografts applied to the wound (F) Twelve months after skin grafting surgery.

## 3. Discussion

The necessity of a long waiting period before skin grafting is a major concern in the use of an artificial dermis for the treatment of large skin defects. The waiting period for traditional artificial dermises is reported to be 3–4 weeks. For example, Opoku-Agyeman et al. reported a systematic review and analysis of 13 studies (31 patients) using Integra® for reconstruction after nevus excision, with a waiting period of 3.28 ± 0.83 weeks [6]. Hicks et al., in a systematic review of the literature on the use of Pelnac® in the treatment of burns, reported that the mean waiting time for skin grafting in 72 studies (1084 patients) was 24.2 days (range 0–80 days) [5]. In contrast, the mean waiting period of this study was approximately 2 weeks, which is shorter than that of previous studies that did not impregnate bFGF into the artificial dermis, suggesting that the use of bFGF-impregnated CGS allows for a shorter waiting period for skin grafting compared to the traditional artificial dermis. As this study lacked a control group of non-bFGF impregnation, a prospective randomized control study with more cases is required to strengthen the evidence of the waiting-period shortening effect of bFGF impregnation on the artificial dermis. Matsumine et al. used bFGF-impregnated CGS to treat eight acute wounds with exposed bone, cartilage, or tendon. Five patients underwent two-stage skin grafting with a waiting period of 22 ± 4 days [23]. Although their waiting period was longer than ours, they noted that many of their cases had poor blood flow in the wound bed and that more cases with comparable wound bed status would be needed to show the effect of bFGF in reducing the waiting period.

Another concern was the risk of infection during the waiting period. The waiting period is not only burdensome to the patient but also increases the risk of infection, as the collagen sponge is a foreign body before granulation, with no capillary invasion [7,8]. According to a report by Gonzalez et al., the infection rate was 16.8% in a review of 1254 cases involving Integra® and other artificial dermises [24]. Though we expected that a shorter waiting period would contribute to a lower infection rate, we could not prove it. Infection was established one week after the implantation of the bFGF-impregnated CGS, and it was not possible to perform skin grafting earlier. However, the infection can be managed with known treatments, including removal of the silicone sheet, washing, and administration of antibiotics. Infection was not negligible, but it did not affect the success rate of the skin grafting.

Treatment with artificial dermis has a satisfactory effect on scar revision and may be a promising treatment for scar control and prevention [25]. In addition, some reports have revealed that bFGF application significantly improves scar quality [26–28]. The use of bFGF-impregnated CGSs is expected to improve scar quality. In this study, the mean VSS score of 6.07 was acceptable, compared to the previous study by Shang et al. who investigated cases of artificial dermis combined with autologous split-thickness skin grafting in 28 burn patients; they reported that the mean VSS was 5.24 ± 0.76 at 10 months after skin grafting [19]. However, since the present study has limitations, including different skin grafting methods (mesh or sheet), variation in the location of target lesions, and varied follow-up periods, further studies are required to determine whether bFGF-impregnated Pelnac Gplus® improves scar quality.

In conclusion, skin grafting was successfully performed approximately two weeks after implantation of the bFGF-impregnated CGS, suggesting that bFGF impregnation may shorten the waiting period without decreasing the success rate of skin grafting. The incidence of infection was similar to that reported in previous studies using a traditional artificial dermis. Further research should be conducted to strengthen the evidence of the waiting-period shortening effect and scar quality improvement effect of bFGF impregnation on the artificial dermis.

## Declaration of competing interest

None.

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