

Selection of Artificial Dermis for Shortening Treatment Period: Integra versus Pelnac

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Background: Skin reconstruction of full-thickness skin defect wounds using artificial dermis is performed using secondary split-thickness skin grafting. For the selection of artificial dermis to shorten the treatment period, the waiting time until secondary skin grafting was investigated when the dermis-like tissue was constructed with Pelnac or Integra.

Methods: We evaluated 26 patients who underwent secondary skin grafting after dermis reconstruction with Pelnac (18 patients) or Integra (8 patients) for full-thickness skin defects between 2006 and 2017. The waiting period from artificial dermis application to closure of the full-thickness skin defect with a secondary skin graft was investigated retrospectively.

Results: Skin grafts survived well in all cases, and no complications of grafts or donors were observed. The mean waiting period was 17.5 ± 4.2 and 22.0 ± 4.6 days for the Pelnac and Integra groups, respectively (significantly shorter in the Pelnac group).

Conclusions: The difference in waiting period is presumed to be due to the structural differences between the collagen sponge layer, which is the dermal replacement layer of Pelnac and Integra grafts. In cases where shortening the treatment period is important, Pelnac should be the first choice. In addition, in pediatric cases and widespread burns where it is difficult to control the infection during the waiting period, Pelnac is considered to be the first choice because the risk can be reduced by shortening the waiting period. (*Plast Reconstr Surg Glob Open* 2021;9:e3599; doi: [10.1097/GOX.0000000000003599](https://doi.org/10.1097/GOX.0000000000003599); Published online 10 June 2021.)

INTRODUCTION

Artificial dermis is a general artificial material with a 2-layer structure in which collagen derived from pigs and cows is synthesized into a sponge shape and a silicon sheet is attached to the surface layer. When an artificial dermis is attached to a full-thickness skin defect, fibroblasts and new blood vessels invade it using the collagen sponge layer of the artificial dermis as a scaffold to produce collagen fibers and construct a dermis-like tissue. High-quality reconstruction is possible by performing split-thickness skin grafting on the surface layer of the constructed dermis-like tissue. In 1980, Yannas and Burke¹ reported the concept of artificial skin developed to cover full-thickness skin defects after debridement in

patients with extensive burns. In 1981, Burke et al² first clinically applied artificial dermis to severe burns in children and reported its usefulness. Furthermore, the development of artificial dermis has been widespread. Even in Japan, Suzuki et al³ developed their own 2-layer artificial dermis, which was approved in Japan as Pelnac (Gunze, Tokyo, Japan) in 1995 and is used clinically. The artificial skin of Yannas and Burke¹ was approved and released in the United States in 1996 as Integra (Integra Lifesciences Corporation, Princeton, N.J.).

The collagen sponge layer, which is a dermal replacement layer of Pelnac, is made by processing atelocollagen derived from pig skin into a sponge shape and supplied in a vacuum freeze-dried state. However, that of Integra is a cross-linked type I collagen derived from the Achilles tendon of cows with glycosaminoglycan, and has a denser structure compared with that of Pelnac. The 2-layer artificial dermis requires a certain waiting period of about 2–3 weeks after application to a full-thickness skin defect until a dermis-like tissue is formed that enables secondary skin grafting. In clinical experience, Integra had a longer waiting period than Pelnac. However, to date, few studies have evaluated the waiting period based on the type of artificial

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dermis, and a definitive opinion has not been reached. The selection of artificial dermis is related to the treatment period of full-thickness skin defect. Therefore, this study was conducted as 1 of the selection criteria for artificial dermis to shorten the treatment period. We report a retrospective study of the waiting period until secondary skin grafting for cases with full-thickness skin defects treated by skin grafting after construction of dermis-like tissue using Pelnac or Integra.

MATERIALS AND METHODS

From 2006 to 2017, 26 patients (15 men, 11 women; age range: 1–87 years; mean age \pm SD: 44.5 \pm 27.2) who underwent dermis reconstruction with Integra or Pelnac followed by 2-stage skin grafting were included in this study. Each artificial dermis was attached to the skin defect. When a dermis-like tissue capable of skin grafting had formed, skin grafting was performed in 2 stages. After visually confirming that a red dermis-like tissue was constructed in the case of Pelnac and a vanilla-colored dermis-like tissue in the case of Integra, it was judged that a dermis-like tissue capable of secondary skin grafting was formed. Cases in which basic fibroblast growth factor (bFGF) or negative pressure wound therapy was applied after artificial dermis application were excluded. In addition, wounds smaller than 2 cm that could be expected to close without a 2-step skin graft were excluded. The causes of the skin defect included after tumor resection (8 cases, 30.8%), trauma (4 cases, 15.4%), burn (3 cases, 11.5%), scar resection (3 cases, 11.5%), nevus resection (3 cases, 11.5%), leg ulcer (2 cases, 7.7%), flap donor site (2 cases, 7.7%), and after inflammatory skin disease resection (1 case, 3.9%). The size of the wound of the full-thickness skin defect was calculated from the major axis and the minor axis. Patients were informed about the potential risks and benefits of all treatment options. Written informed consent was obtained from all patients or from their parents. Statistical processing was performed using the Mann-Whitney *U* test and Spearman's rank correlation coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

Integra was applied to 8 patients and Pelnac to 18 patients (Table 1). The average age of each case group was 45.6 (24–85) and 54.4 (1–87) years, respectively (not significantly different). There was also no difference between the groups in terms of diseases that affect wound healing, such as diabetes, radiation, and smoking. The mean wound size was 70.3 \pm 61.0 cm² and 99.0 \pm 62.4 cm² for the Integra and Pelnac groups, respectively. There was no significant difference in the wound size between the 2 groups. There was no correlation between the wound size and waiting time. Skin grafts were engrafted in all cases. No other complications were found at the skin graft or donor site. The mean waiting time was 22.0 \pm 4.6 days and 17.5 \pm 4.2 days for the Integra and Pelnac groups, respectively. The waiting period was significantly shorter in the Pelnac group ($P = 0.0464013$; Fig. 1).

Table 1. Overview of Waiting Period until Skin Grafting in Integra and Pelnac Groups

Patient	Age (y)	Pathology	Wound Localization	Wound Size (cm ²)	Dermis-like Tissue Construction Period
<i>Integra Group</i>					
1	24	Burn	Upper arm	200	20
2	85	Burn	Head	150	21
3	26	Scar	Forearm	112	21
4	38	Tumor	Hand	21	20
5	71	Scar	Finger	65	21
6	32	Trauma	Forearm	144	33
7	63	Tumor	Forearm	60	22
8	26	Trauma	Knee	40	18
<i>Pelnac Group</i>					
1	1	Nevus	Face	150	11
2	68	Tumor	Finger	60	21
3	53	Scar	Forearm	160	17
4	1	Nevus	Face	131	12
5	81	Trauma	Finger	6	22
6	3	Nevus	Face	56.5	14
7	35	Inflammatory	Chest	150	26
8	49	Burn	Forearm	150	14
9	77	Tumor	Finger	21.45	22
10	69	Tumor	Face	7.8	14
11	68	Flap donor site	Chest	140	17
12	73	Skin ulcer	Foot	77	21
13	52	Skin ulcer	Knee	90	20
14	59	Tumor	Face	9	13
15	62	Trauma	Head	24	17
16	62	Tumor	Head	16.8	21
17	70	Flap donor site	Face	12.8	19
18	87	Tumor	Face	3.6	14

Case 1

A 26-year-old woman suffered a third-degree burn on her left knee from a hot liquid. Surgery was performed 11 days after the injury (Fig. 2A). Debridement of necrotic tissue resulted in a 5 \times 8 cm full-thickness skin defect. Integra was attached to the wound. Adipose tissue on the wound surface could be seen through the Integra silicon sheet (Fig. 2B). On day 18 after artificial dermis application, skin grafting was performed because dermis-like tissue had been constructed. When the Integra silicon sheet was removed, a vanilla-colored dermis-like tissue was formed on the wound surface, although some red parts remained (Fig. 2C). A thicker split-thickness skin graft was performed from the left inguinal region (Fig. 2D). At 13 months after skin grafting, the skin survived well and there were no complications, such as hypertrophic scars or contractures (Fig. 2E).

Case 2

A 69-year-old man underwent resection of a basal cell carcinoma of the nose, resulting in a 3 \times 2.6 cm full-thickness skin defect (Fig. 3A). Pelnac was attached to the wound to evaluate the stump of the resected specimen by pathological examination (Fig. 3B). At 14 days after artificial dermis application, skin grafting was performed when the dermis-like tissue had just been worn. When the Pelnac silicone sheet was removed, a red dermis-like tissue resembling granulation tissue had formed on the wound surface. In addition, contraction of the skin defect was observed (Fig. 3C). A thicker split-thickness skin graft was performed from the anterior

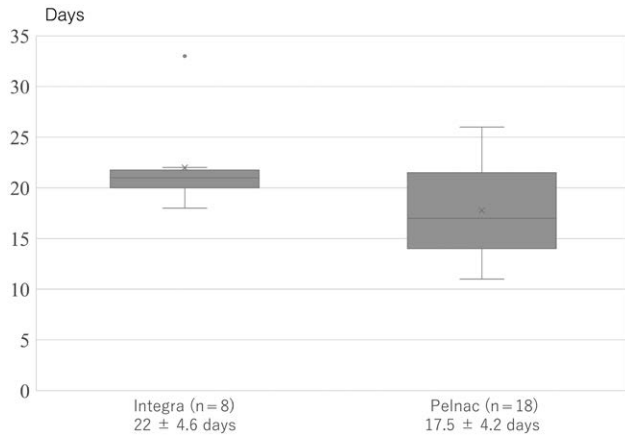


Fig. 1. Waiting days in the Integra and Pelnac groups.

part of the right ear (Fig. 3D). At 3 years and 6 months after skin grafting, the skin survived well and there were no complications, such as hypertrophic scars or contractures (Fig. 3E).

DISCUSSION

Artificial dermis is a material material that can obtain good functions and cosmetic results after 2-stage skin grafting on the surface layer of thick dermis-like tissue.⁴ To date, artificial dermis has been applied to traumatic skin defects, burns, tumors, nevus, and full-thickness skin defects, such as flap donor sites. In this study as well, its application was indicated for various primary diseases.

Yannas and Burke,¹ who first reported artificial dermis, launched Integra in the United States in 1996. Integra is formed from type I collagen derived from bovine tendons and chondroitin 6 sulfate derived from sharks, which is a type of glycosaminoglycan, to prevent degradation by collagenase. Its average pore size is 70–200 μm. The product is immersed in phosphate buffered saline and is in a wet state. It has a thickness of approximately 2mm and is harder than Pelnac. The surface silicon film is also harder than Pelnac. Immediately after applying Integra, the wound surface tissue can be seen through it. After that, it changes to a cream color in approximately 1 week. Furthermore, in approximately 3 weeks, vanilla-colored dermis-like tissue is formed that enables skin grafting.



Fig. 2. Integra application case. A 26-year-old woman with burn on the left knee. A, 11 days after the injury. B, Integra attached to the wound. C, Eighteen days after Integra application. D, After skin grafting. E, Thirteen months after skin grafting.

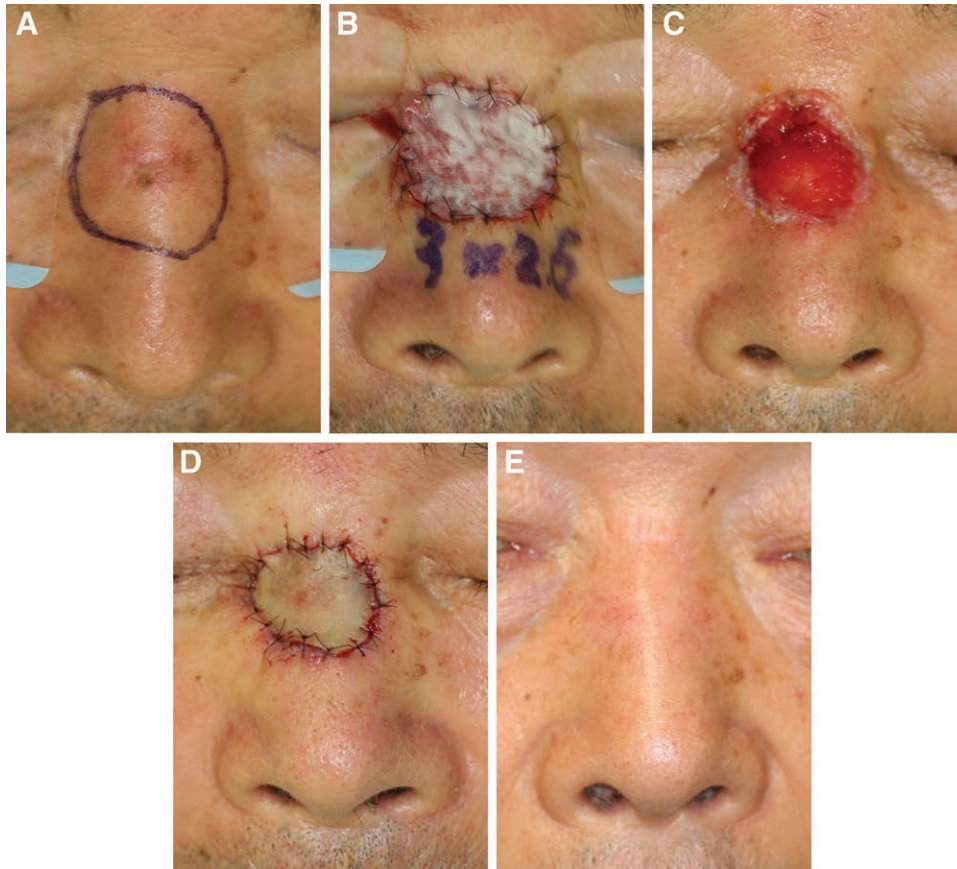


Fig. 3. Pelnac application case. A 69-year-old man with basal cell carcinoma of the nose. A, Before tumor resection. B, Pelnac attached to the wound. C, Fourteen days after Pelnac application. D, After skin grafting. E, Forty-two months after skin grafting.

Suzuki et al³ developed the Pelnac graft in 1995. Pelnac is formed by adding thermal and chemical cross-links to atelocollagen derived from porcine tendons. Atecollagen is used to reduce the antigenicity of collagen. The product is made sponge-like by freezing and drying, and is moisturized with physiologic saline before use. Compared with Integra, Pelnac is thinner and more supple, so it is easier to apply to uneven wound surfaces. Immediately after Pelnac application, the layer of atelocollagen becomes thinner due to moisturizing, and the wound surface can be seen through it. Dermis-like tissue forms in 2 weeks to allow skin grafting. The dermis-like tissue becomes a red wound surface similar to granulation tissue, in contrast to the vanilla-colored tissue formed by Integra. There is a clear macroscopic difference between the 2 dermis-like tissues.

In vitro and in vivo comparisons between Integra and Pelnac have been reported.⁵⁻⁷ In animal experiments, no difference was reported in thickness of the dermis-like tissue, infiltration of inflammatory cells, and degree of angiogenesis at 9 days postoperatively.⁷ In vitro studies have reported that Pelnac contracts more than other artificial dermis grafts.⁵ However, in a clinical study comparing Integra and Pelnac, the wound was significantly contracted by Pelnac up to 4 weeks postoperatively, but there was no difference between the two grafts at 1 year postoperatively, and Pelnac was superior in scar quality.⁶ For wounds with a

depth of ≥ 1.5 cm, Integra shortens the time to wound closure, and Integra is recommended for use in deep wounds.⁶ In other words, these studies suggest that there is little histologic difference between Integra and Pelnac, and there is no significant difference between them. However, in all studies, examination of the dermis-like tissue construction period until skin grafting becomes possible is insufficient.

Artificial dermis is a useful method for treatment of full-thickness skin defects, but 2-3 weeks are required from application of the artificial dermis until dermis-like tissue is constructed. As a result, the treatment period is lengthened, and the risk of wound infection is increased. Infection of the area where the artificial dermis is applied makes secondary skin grafting difficult and further prolongs the treatment period. To shorten the dermis-like tissue construction period, other methods, such as addition of growth factors and cells to the artificial dermis and improvement of the artificial dermis itself, have been attempted. Formation of dermis-like tissue is reportedly promoted by using bFGF, vascular endothelial cells, and mesenchymal stem cells.⁸⁻¹⁰ We also reported that addition of dedifferentiated fat cells, which are similar to mesenchymal stem cells, promotes vascular invasion into the artificial dermis.⁹ The addition of dedifferentiated fat cells reportedly formed an anchoring fibril of the epidermal dermis adhesive layer at the early 2 weeks after application

of the artificial dermis.¹¹ Furthermore, the effect of shortening the construction period of dermis-like tissue by using negative pressure wound therapy together has been reported.¹² Therefore, in our study, cases using bFGF preparations or negative pressure wound therapy, which can cause bias for comparison of the dermis-like tissue construction period, were excluded.

Regarding the improvement in artificial dermis, Integra has developed a product in which the collagen layer is thinned to approximately 1 mm as a single layer for 1-stage skin grafting. Reportedly, skin grafts survive even if skin grafting is performed at the same time as application of a thin artificial dermis.^{13–15} However, in 1-stage skin grafting, the possibility of poor engraftment and severe wound contraction with products that have a thin collagen layer should be examined. In other words, the indication may be limited in the treatment of exposed parts and scar contracture where the contraction of skin graft pieces is a problem. On the other hand, the manufacturers of Pelnac have developed a new product impregnated with alkali-treated microbeads while maintaining the thickness of the collagen sponge layer.¹⁶ It has been reported that the combined use of a 7–14 $\mu\text{g}/\text{cm}^2$ bFGF preparation with this Pelnac material promotes the sustained release of bFGF over a long period of time and promotes the construction period of dermis-like tissue.¹⁶

There may be some possible limitations in this study. First, there was a significant difference between the 2 groups; however, the number of samples was small. Second, this study was a retrospective one, and the selection criteria for artificial dermis were not clear. In addition, the judgment that the formation of the dermis-like tissue is completed was mainly based on the appearance of the wound and was a subjective evaluation. The development of an objective evaluation method is also desired in clinical practice.

CONCLUSIONS

To date, studies on shortening the construction period of dermis-like tissue by artificial dermis have been widely conducted, but comparative study of the waiting period until skin grafting has been insufficient. We suggested that the time to secondary skin grafting was significantly shorter using Pelnac, and the treatment period for wounds could be shortened compared with that for Integra. In cases where shortening the treatment period is important, Pelnac should be the first choice. However, further consideration is needed when the required tissue thickness is important. In addition, in pediatric cases and widespread burns where it is difficult to control the infection during the waiting period, Pelnac is considered to be the first choice because the risk can be reduced by shortening the waiting period.

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