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ARTICLE

Clinical experience of the use of Integra in combination with negative pressure wound therapy: an alternative method for the management of wounds with exposed bone or tendon

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ABSTRACT

The use of Integra has attracted great interest in the treatment of wounds with exposed bone or tendon, which may lead to associated morbidities. However, the use of Integra alone results in poor wound outcomes. We conducted a randomized clinical study to evaluate the combined effects of Integra and negative pressure wound therapy (NPWT). Thirty-six patients with wounds with exposed bone or tendons were treated with Integra alone and with a combination of Integra and NPWT ($n = 18$ respectively). Negative pressure (125 mm Hg) was applied intermittently till Integra was revascularized. The take rate of Integra and time taken from Integra coverage to skin transplantation was recorded for each case. The average take rate of Integra in the conventional treatment group (Integra with partial packing compression dressings) was lower than that for the new treatment group (Integra with NPWT) ($p < 0.001$, 95% CI: 6.44–0.20). The mean time period from Integra coverage to skin transplantation was longer for the conventional treatment group than for the new treatment group ($p < 0.001$, 95% CI: −13.18 to −11.24). The application of NPWT could potentially increase the take rate of Integra and shorten the duration of hospital stay. The use of Integra with NPWT could be a treatment option for wounds with exposed bone or tendon.

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KEYWORDS
Integra; take rate; time; negative pressure wound therapy

Introduction

The number of patients with large areas of soft tissue defects with exposed bones or tendons has increased recently due to an annual increase in car accidents, wounds derived from high-energy explosives, work-related injuries, and trauma caused by tumor resection. Such wounds, often associated with severe avulsion, severe infection, and poor blood supply make wound repair difficult [1]. Methods of wound reconstruction include skin grafting, local flaps, and free tissue transfer [2]. Local or free flaps are rarely chosen because of large-area tissue defects and surrounding harming vessels [3]. With traditional wound therapy such as petrolatum gauze healing time is long and the rates for complications such as wound infection, bone fracture, and non-union, osteonecrosis, osteomyelitis, and fistula formation, are relatively high [4]. Therefore, it is of great significance to develop efficacious and simple treatments for exposed bone or tendon wounds.

Integra is composed of an upper layer of silicone sheet and a lower layer of collagen sponge and has been used to treat severe burn injuries since the 1990s [5]. The Integra consists of an inner layer of collagen and chondroitin-6-sulfate and a temporary silicone epidermal substitute (average 21 days), which allows the migration of fibroblasts, macrophages, lymphocytes, and capillary ingrowth onto the surface to regenerate the dermis. Recently, Integra has been widely used for the treatment of skin defects after a traumatic injury, tumor resection, and chronic wounds [6]. It is found that when Integra is implanted into a full-thickness skin defect, fibroblasts and capillaries around the wound infiltrate it, the collagen sponge biodegrades and is replaced by host dermis similar to granulation tissue within a few weeks (average 21 days) before secondary split-thickness skin grafting is performed [7]. However, a long waiting time before secondary skin grafting and a relatively high incidence of infection when used on chronic wounds are important concerns in using conventional Integra [8].

Negative pressure wound therapy (NPWT) is frequently used to accelerate acute and chronic wound healing [9]; an open-cell polyurethane sponge is clipped and placed in the wound, sealed with an adherent drape, and then attached to a tube, through which continuous sub-atmospheric pressure is applied. This system removes fluid from the wound, decreases edema, improves local blood flow, enhances neovascularization, and decreases bacterial counts. It is also a useful method to stabilize the underlying graft due to these properties and has the ability to conform to the shape of any wound to maintain contact of the graft with its bed and minimize shear forces. It was reported that the application of sub-atmospheric pressure increases vascularization and aids in the incorporation of Integra in a variety of wounds that would otherwise have required more extensive reconstructive efforts [10,11]. However, it was not entirely clear whether the decrease in the rate of infection and take rate of Integra were attributable solely to negative pressure wound therapy because previous studies included more than one variable or were case reports [12]. In the present study, we studied the rate of infection and take rate of Integra combined with negative pressure wound therapy and compared the results to those of our previous study on the use of Integra with compression dressings.

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Patients and methods

This study followed a randomized design with an observation period. Thirty-six patients (from May to September 2015) were recruited and divided into 2 groups: the new treatment group ($n = 18$) and the conventional treatment group ($n = 18$). Eighteen patients were randomized for treatment with Integra and negative pressure wound therapy for tissue reconstruction (new treatment group), while the other patients were randomized to undergo reconstruction with Integra and compression dressings in our clinical practice(conventional treatment group) (Table 1). All men were smokers and all women were non-smokers. The ethics committee at our institution approved the study. The patients provided their written informed consent before the start of the study.

Surgical techniques

Integra was grafted after the wound was debrided completely either immediately after excision or after debridement. A preconditioning procedure could have been done with negative-pressure techniques. An Integra coverage was then performed using two different techniques. The first was the conventional technique in our previous studies, Integra was adapted to the wound size and shape and then stapled to the wound edge. Postoperatively, partial packing compression dressings above the level of the grafted Integra were used to support the fixation. A strict post-surgical surveillance protocol was used to monitor for infection and hematoma which included sterile dressing changes at regular intervals. In case of an infection, the infected part of the Integra was excised, cleaned and compression dressings were applied again. After full Integra neovascularization, the patients returned to the operating room for a skin transplant. The second method combined Integra with NPWT in this study. Integra was adapted to the wound shape and size, and a negative-pressure dressing was then applied to the Integra. The protocol for the negative-pressure therapy involved applying a negative pressure of 120 mm Hg, intermittently (suction cycles; on for 5 min and off for 2 min). The vacuum dressing was sealed with the foils provided. The dressing was changed every fourth or fifth day postoperatively and the negative-pressure drainage was done every day to limit the infection and hematoma of the Integra. The patients returned to the operating room for a skin transplant after full Integra revascularization.

Measures and statistics

The parameters assessed included the following: demographic characteristics, take rate, and time from Integra coverage to skin transplantation. The take rate was determined by an experienced surgeon who traced and determined the nonintegrated area in relation to the total grafted Integra area. Statistical analysis was performed using SPSS on the data with the *t*-test. $p < 0.05$ was considered significant.

Results

Thirty-six patients were included in our study. (Table 1) The mean age was 40 years (ages 21–56 years) in the new treatment group and 42 years (ages 23–58 years) in the conventional treatment group. ($p = 0.54$) The distribution of sex, wound location, and cause of injury were similar in the two groups. In the conventional treatment group, three patients had a pre-existing disease; one had diabetes mellitus, another had coronary artery disease,

Table 1. Demographic characteristics of the patients.

Patient no./sex/age (years)		Pre-existing disease		Would location		Size of would (cm/cm^2)		Integra take (%)		Time until skin graft (days)	
New group	Conventional group	New group	Conventional group	New group	Conventional group	New group	Conventional group	New group	Conventional group	New group	Conventional group
1/M/41	1/F/43	N	N	Right thigh	Right leg	10 × 8 (80)	10 × 9 (90)	100	89	7	19
2/M/45	2/M/39	N	N	Left leg	Right planter pedis	11 × 9 (99)	12 × 9 (108)	100	92	9	20
3/M/23	3/M/26	N	N	Left foot dorsum	Left leg	12 × 8 (96)	11 × 8 (88)	100	94	8	18
4/F/38	4/F/58	N	Diabetes mellitus	Right leg	Right thigh	10 × 10 (100)	10 × 10 (100)	100	0	10	0
5/M/21	5/M/40	N	N	Left planta pedis	Left leg	12 × 11 (132)	12 × 10 (120)	100	93	9	23
6/M/54	6/M/23	Diabetes mellitus	N	Right thigh	Left thigh	12 × 9 (108)	12 × 10 (120)	95	94	11	22
7/F/43	7/M/48	N	N	Left thigh	Right planta pedis	13 × 8 (104)	13 × 7 (91)	100	95	9	21
8/M/57	8/M/57	N	N	Right leg	Left foot dorsum	14 × 7 (98)	12 × 7 (84)	96	90	8	23
9/M/50	9/F/55	Coronary artery disease	Coronary artery disease	Left foot dorsum	Left leg	11 × 8 (88)	11 × 9 (99)	95	80	9	20
10/F/35	10/F/49	N	Hypertension	Right planta pedis	Left thigh	10 × 9 (90)	10 × 9 (90)	100	90	9	19
11/M/25	11/M/31	N	N	Left leg	Left thigh	12 × 9 (108)	11 × 9 (99)	100	92	8	20
12/M/37	12/M/45	N	N	Left planta pedis	Left leg	10 × 9 (90)	10 × 9 (90)	100	89	10	24
13/M/33	13/M/29	N	N	head	Right leg	10 × 7 (70)	10 × 8 (80)	100	88	8	21
14/F/29	14/F/30	N	N	Left thigh	Left leg	11 × 7 (77)	11 × 8 (88)	100	90	7	20
15/M/48	15/M/48	N	N	Left leg	Right foot dorsum	12 × 8 (96)	12 × 8 (96)	98	92	8	21
16/M/46	16/M/46	N	N	Right leg	Right leg	14 × 6 (84)	14 × 7 (98)	97	91	7	22
17/F/33	17/F/33	N	N	Left planter pedis	Right thigh	14 × 7 (98)	12 × 7 (84)	100	90	9	21
18/M/56	18/M/56	Hypertension	N	Right leg	Right leg	11 × 8 (88)	11 × 9 (99)	94	0	10	0

New group: the new treatment group; conventional group: the conventional treatment group; F: female; M: male; N: no.

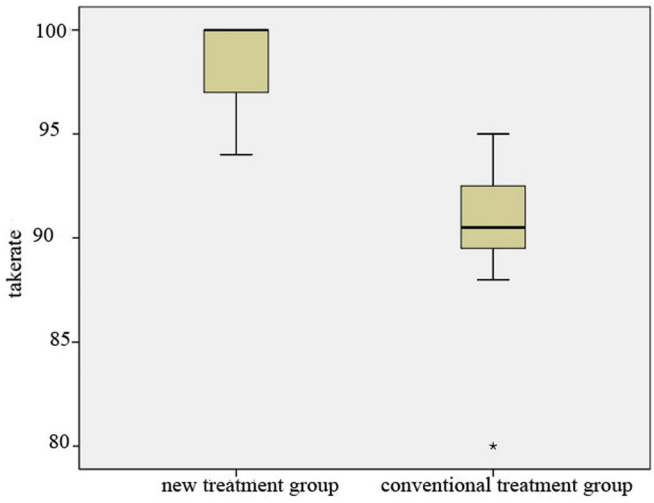

Figure 1. Mean take rate for the new and conventional treatment group. Compared with the conventional treatment group, the new treatment group demonstrated a significantly higher take rate ($p < 0.001$).

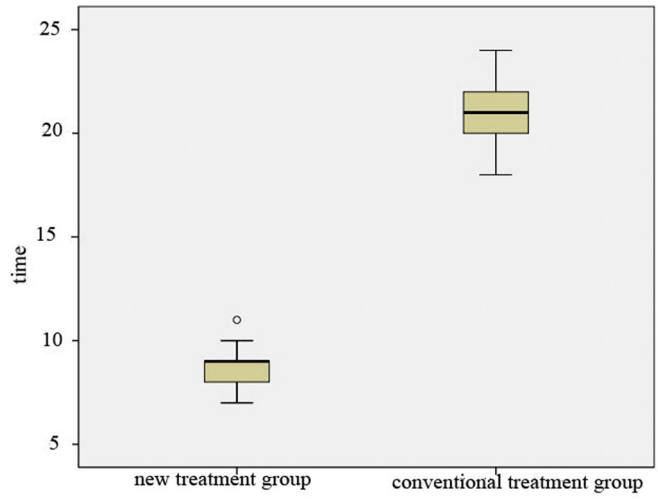

Figure 2. Mean days between Integra application and skin grafting: New and conventional treatment group. Compared with the conventional treatment group, the new treatment group demonstrated a significantly shorten time between Integra application and skin grafting ($p < 0.001$).

and a third had hypertension. In the new treatment group, three patients had pre-existing diseases similar to those in the conventional group. The wounds covered with Integra had a mean size of 95.78 cm^2 (range 80–120 cm^2) in the conventional treatment group and 94.78 cm^2 (range, 70–132 cm^2) in the new treatment group (Table 1). There were no significant differences between the two groups with respect to the size of wounds ($p = 0.81$). The extra costs with the Integra with NPWT of every patient in the new treatment group was mean 500 dollars.

All patients demonstrated good Integra take rates (94–100%) in the new treatment group. The average take rate was 93% in the conventional treatment group and 99% in the new treatment group and the average take rate of Integra in the conventional treatment group was lower than that for the new treatment group. ($p < 0.001$) (Figure 1). This different rate of infection between the two groups was reflected. Two patients (fourth and eighteenth patient respectively) in the conventional treatment group without NPWT developed serious infections and loss of all Integra, while 6 patients in the new treatment group with NPWT developed minimal infection signs at the wound edges. A significant difference was found in the period from Integra coverage to skin graft between the two groups. The mean duration from Integra coverage to skin transplant was 21 days for the conventional treatment group, and an average of 9 days for the new treatment group and the mean time period was longer for the conventional treatment group than that for the new treatment group ($p < 0.001$) (Figure 2). The decrease in the duration between Integra cover and skin transplant resulted in shorter hospital stays. Figure 3 shows a case from the new treatment group.

Discussion

Reconstructive surgery plays a very important role in wound closure. According to the reconstructive ladder, methods are currently evolving to achieve satisfactory wound closure within the least time [13]. Among reconstructive ladder methods, a skin graft may be the simplest option which is associated with minimal donor-site morbidity and is cost-effective [14,15]. However, skin grafting is unreliable on exposed bones and tendons with previous bed wounds [16]. In our study, due to damage to the wound surroundings, the patients had complex wounds with exposed bone or tendon, which were repaired by skin grafting following the healing of the wounds with Integra.

Integra allowed devitalized tissue to be excised early and wounds were covered immediately in patients with severe burn injuries [17]. Integra is a porous collagen/chondroitin-6-sulfate fibrillar material with an epidermis-like silastic sheet. Stimulation of the three-dimensional dermal structure by the collagen/glycosaminoglycan matrix promotes the migration of cells (e.g. fibroblasts and endothelial cells) from the surrounding tissue of the wound into the fiber network where a neodermis is created similar to the natural dermis with respect to histological and functional features. Integra has low antigenicity and it decreases host inflammatory responses [18]. To provide a good matrix for cellular and vascular replacement, cells in the dermal template interact with wounds to increase fibroblast attachment and produce a new connective dermal tissue matrix. The neodermis biodegrades gradually and is replaced with normal host collagen without scar tissue. To ensure complete healing of the wound, the epidermis could be simply replaced with a thin skin graft in the second operation during the 21 days after Integra was used in the previous procedure [7]. According to the previous studies, this period until Integra was totally integrated and covered by the epidermis was approximately 21–28 days [19]. This prolonged time period increased the hospital cost (mean extra cost: $500) and the risk of infection. So the hospital cost between the two groups was almost the same. It has been reported that a good fix and complete neovascularization of Integra could decrease the time period. In this study, NPWT helped connect the Integra to the wound bed, and the time interval was decreased by more than half. Furthermore, we also found that the take rate had significantly improved with the use of NPWT (99 vs. 93, $p < 0.001$). There were no patients with serious infections whereas 2 patients from our previous study had lost all the Integra because of infection. In previous studies, the effect of the NPWT could not be found out due to other confounding variables [12]. However, in this study, it was clearly demonstrated that the positive effects of rapid wound healing and integration of Integra were attributable to NPWT due to the absence of any other variable. In theory, an NPWT aids Integra to integrate with host tissue by a combination of the following mechanisms. First, excess interstitial

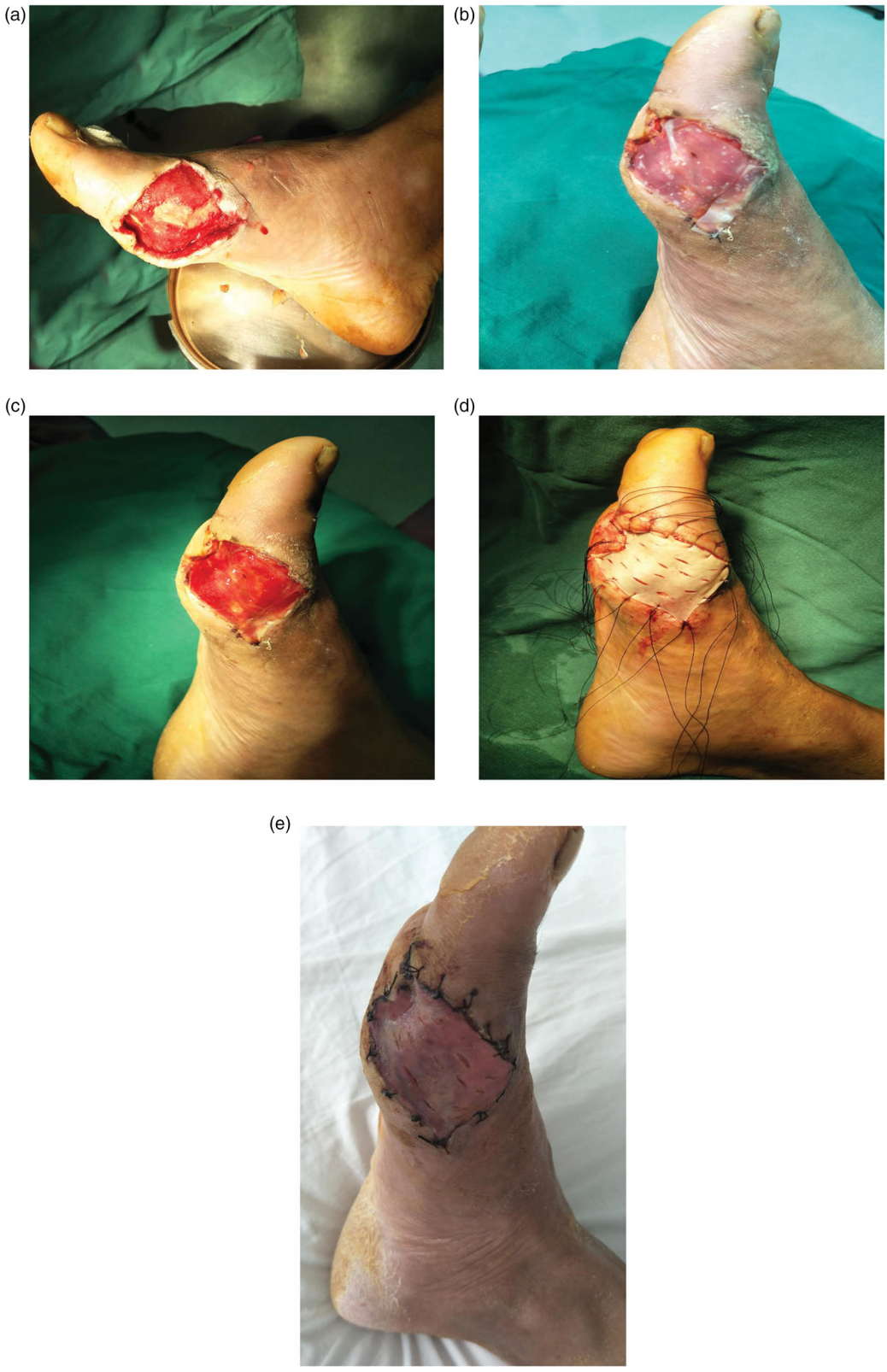

Figure 3. A 50-year-old man with a tendon-exposed wound on the left foot after the new treatment. (a) Wound status before Integra grafting; (b) shaping Integra and covering the tendon-exposed area; (c) multiple fresh granulation tissue on the tendon-exposed wound bed 8 days postoperatively; (d, e) the skin grafts surviving after full-thickness skin transfer for 9 days.

fluid could be removed under the Integra to allow for decompression of small blood vessels surrounding the wound [20], which resulted in increased perfusion, oxygen, and nutrient delivery to the central part of the wound, which promotes the faster formation of dermal tissue. Second, the suction of an NPWT may have removed bacteria as there was no infection among the patients on NPWT [21]. Third, the NPWT might have mediated the factors that help cellular proliferation and protein synthesis [22].

However, in this study, we did not focus on the aesthetics and scarring after skin integration at follow-up. It was hypothesized that due to the enhanced dermal tissue formation of Integra, a superior aesthetic and functional outcome could be gained, and which could be analyzed in future studies. And the other disadvantage of the study was that no biopsies were made to analyze the mechanism of this study which we would further perform in the future.

Conclusions

The use of Integra with NPWT can be an option for an exposed bone or tendon wound where flap surgery is not possible due to inadequate donor sites or poor general conditions where major surgery is contraindicated.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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