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ORIGINAL STUDY

Outcomes following extremity wound coverage with an acellular skin substitute (Integra) : a multi-center study

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The purpose of this manuscript is to document results and complications of use of a regenerative dermal matrix skin substitute for coverage of extremity wounds. A retrospective review at 3 institutions identified 28 patients and 34 wounds who had undergone use of this material (Integra). Complications included failure in two patients (4 wounds). However, overall "take" of the regenerative matrix was 86.1%. In most cases, a split thickness skin graft was applied on average at 25 days following the initial procedure. Failures were associated with infection and irradiation of the surgical field. In this series, use of the dermal regenerative matrix was associated with a high rate of success for wound coverage, obviating the need for flap coverage or prolonged dressing changes in most cases. Further series are likely to refine the known indications and contraindications to use of this method.

Keywords : Integra ; skin substitute ; wound coverage ; dermal matrix graft.

INTRODUCTION

Soft tissue coverage can be challenging, particularly in the setting of musculoskeletal surgery. Skin grafting may not be appropriate for all soft tissue beds, and is not possible directly over tendons, neurovascular structures, or bone. Previously these wounds had limited reconstructive options, and often surgeons relied upon rotational or pedicled flaps or microvascular free tissue transfer. However, such solutions are subject to tissue availability, donor site morbidity and require sometimes complex surgical and microsurgical procedures further increasing the morbidity of surgery. Such reconstructive options may require flap monitoring for viability and or immobilization. In addition, failures may leave limited options (*7,11,18*).

Recently, an acellular dermal regenerative matrix material (Integra, Integra Life Sciences, Plainsboro, NJ) has been developed to provide a substrate for wound coverage. This material provides a dermal substrate consisting of denatured bovine collagen and shark chondroitin sulfate. It is available as either a monolayer construct or as a bilayer construct with a silastic outer portion The material and biological properties are altered by cross-linking methods and density, pore size, and chondroitin

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6-sulfate content. The silastic portion consists of 0.1 mm thick medical grade silastic, which is designed to control fluid egress to simulate the function of epidermis (*5,16*). It has previously been used for reconstruction of soft tissue wounds, particularly in the setting of burns, with satisfactory results (*6,12,16,20*). Early clinical results have been acceptable, and it has been used in a variety of challenging clinical settings, including exposed bone, irradiated tissue fields, and deep soft tissue defects (*1,3,4,8,10,14,15,17,20,21*). However, few large studies exist evaluating the use of this material in a clinical orthopedic setting. The purpose of our study is to provide a retrospective review of patients treated with this clinical material for purposes of extremity wound coverage in orthopedic practices at three institutions. The material was used in settings where simple primary closure or immediate skin grafting was not possible and free or pedicled tissue transfer would be another option for coverage.

MATERIALS AND METHODS

Following appropriate Institutional Board Review approval obtained at the three institutions involved in this study, (The Mayo Clinic, The University of Minnesota, and UMDNJ-New Jersey Medical School), the authors performed a retrospective review of patients who had undergone application of Integra for indications of soft tissue coverage. All patients from 2006 to 2012 were included in the series. Information from the medical records was extracted including patient demographics (age, gender, co-morbidities which might affect healing including diabetes mellitus, peripheral neuropathy, vascular disease, current smoking status), site and characteristics of wounds, information regarding index, prior and subsequent procedures, complications, and patient-related outcomes. Failures, including cause and complications, were specifically investigated. The data was shared among sites in a de-identified data set in concordance with the Institutional Review Board protocols of each site.

Surgical techniques

The surgical techniques and indications for application of this material have been described previously (*16*). In general, the surgical field is prepared and any nonviable tissue is debrided (Fig. 1). Any active infection or contamination is cleared prior to use (*8,9*). The bilayer dermal substitute is provided in an unmeshed or meshed version ; application is similar. It is applied to the wound, cut to appropriate size, and sutured into place with nylon suture, ensuring that it does not overlap intact skin and that there is no excess or wrinkling of the graft (Fig. 2). If the unmeshed material is used, it may be meshed prior to application or "pie-crusted" with a number 15 blade following application. A bulky soft dressing or bolster is applied ; a negative pressure vacuum assisted closure device is an alternative.

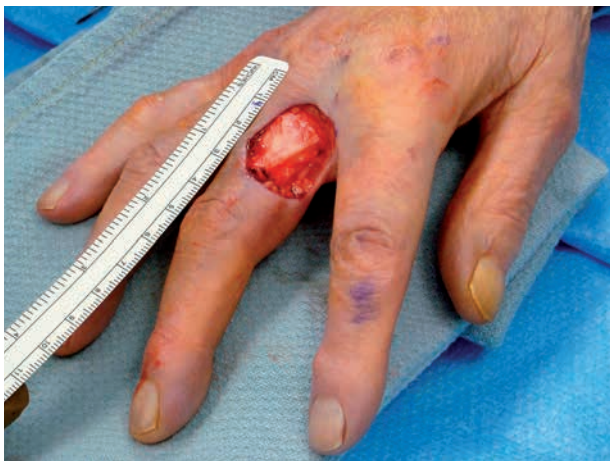

Fig. 1. — The wound is prepared and debrided of any nonviable tissue ; need for additional soft tissue coverage is assessed.

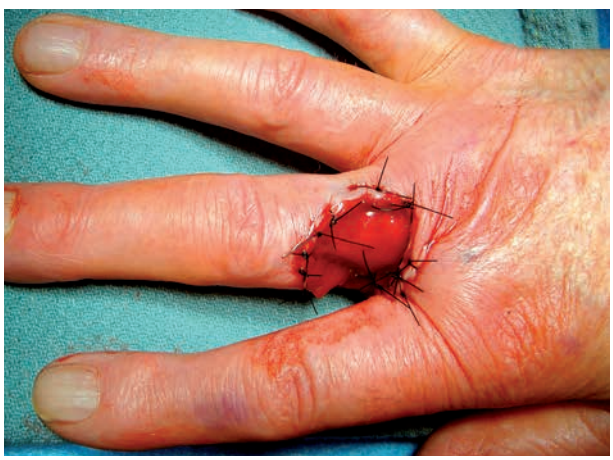

Fig. 2. — After preparation of the wound, the defect is measured and the appropriate sized dermal matrix template cut to size and sutured to the wound.

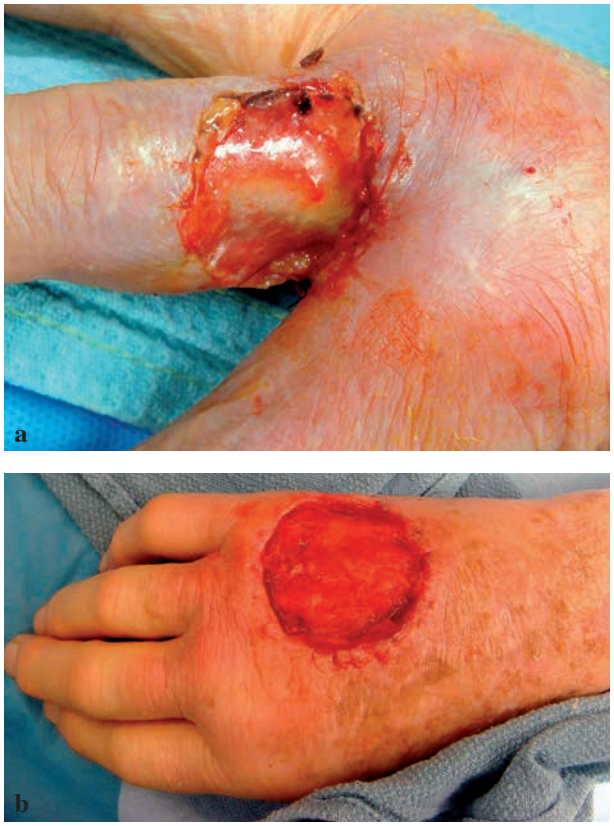

Fig. 3. — The color change to a salmon hue is indicative of the neovascularization and readiness for removal of the silastic template and skin grafting. **a** : same patient as in figures 1 &2 ; **b** : in an elderly man following excision of a large squamous cell carcinoma leaving exposed tendon.

Rehabilitation and monitoring of the wound is similar to other methods of wound coverage and proceeds in the usual fashion. Typically, the color of the wound bed and matrix is monitored. Inosculation and neovascularization has been reported to begin as soon as 24 hours post application, particularly in association with use of negative pressure devices *(2,13)*. Usually, the matrix has good "take" and the wound is ready for a second stage skin graft between 2-4 weeks ; this is marked by the change in color of the wound bed to a yellowish-pink hue *(8,16,19)* (Fig. 3). At this point, the silastic layer may be peeled off and a full or partial thickness skin graft applied (Fig. 4). Alternatively, small defects may be allowed to granulate in over time. Wounds are followed until completion of healing (Fig. 5). Choice of use of bilayer or monolayer, meshed or unmeshed Integra, and timing (if any) of subsequent skin grafting was based upon the discretion of the treating surgeon.

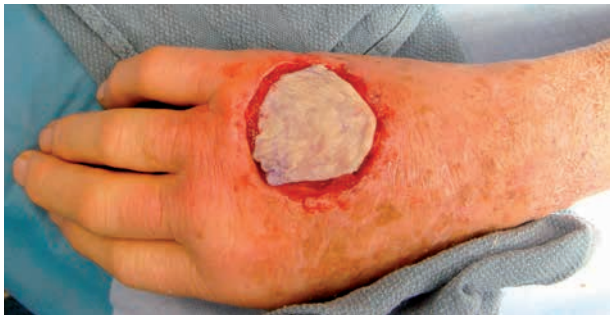

Fig. 4. — A skin graft (either full thickness or partial thickness) may be applied ; alternatively, small wounds may be allowed to granulate in and heal by secondary intent. In this case, a thin full thickness graft was obtained from the upper arm and will be applied as a skin graft.

RESULTS

Twenty-eight patients with 34 wounds underwent application of this material as either a bilayer (n = 11), monolayer (n = 22) or combination (n = 1) for purposes of wound coverage (Table I). There were 21 male and 7 female patients ; average age was 49.5 years (range : 14-85 years). Patients were followed to completion of wound healing in all cases, and follow-up averaged 9.9 months. In two patients (3 wounds), the indication was for post infection soft tissue loss following resolution of the infection ; in one patient and one wound, for soft tissue loss associated with chemotherapeutic extravasation, one patient/wound for scleroderma and exposed PIP joint ; in 23 wounds for traumatic indications, and in six patients/cases for reconstruction following excision of a malignancy. Of these patients, a second stage procedure was performed in 26 cases, at an average time point of 25 days following the initial procedure. The second stage procedure was a thin full-thickness skin graft in two cases, a split thickness skin graft in 24 cases, and the wound was allowed to granulate in or heal by secondary intent in four cases ; while the two patients (4 wounds) with failures had healing with dressing changes and negative pressure vacuum assisted wound closure (n = 1) or additional procedures. The overall complication rate was 21% ; with a major complication (failure) rate of 6.9% (2 patients) and a minor complication rate of 13.8%.

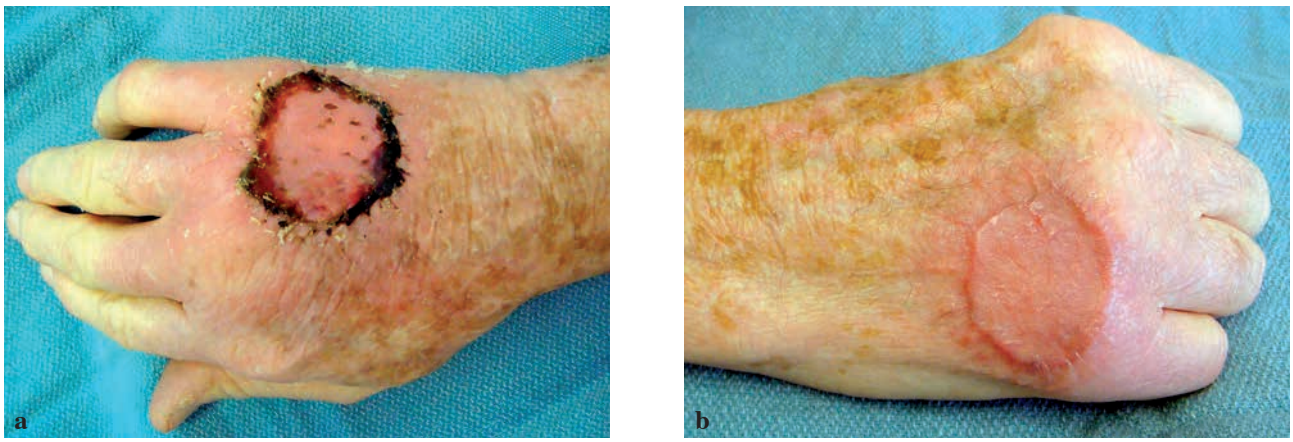

Fig. 5. — The wound is followed until complete healing ; **a** : Same patient as in figure 3b and 4 at 15 days following thin full thickness skin grafting ; **b** : and at 59 days following skin grafting.

Major complications included one patient who was a smoker (3 sites) with infection and failure of his dermal matrix bilayer following his thermal burn and crush injury from a meat packing plant injury ; he eventually underwent rotational and free flaps with adjuvant use of dermal matrix bilayers, which resulted in full coverage and take. Another patient had failure of take and development of severe pain, drainage and soft tissue swelling in one patient with brachytherapy to the site due to primary malignancy. Minor complications included the following : an 83-year-old man with diabetes mellitus had partial failure of take (85% take) ; one patient had delayed healing of the wound over the tibia following application of three monolayers and a bilayer after excision of an osteochondroma ; another patient had a venous bleed under the dermal substitute related to his underlying trauma and digital revascularization.

Because of the small number of complications and failures in the series, we were unable to identify statistically significant predictors of failure.

DISCUSSION

In this manuscript, we describe use of a dermal matrix substitute for use in soft tissue coverage. A high healing rate was noted in this series, with an 86% "take" of the Integra, which is concordant with that seen in other series (*8,17,19*). Of the 34 wounds in this series, failure was noted in 4 wounds (2 patients). These failures were associated with infection and smoking history in 3 wounds (1 patient) who was later successfully treated with a combination of soft tissue coverage techniques including use of the dermal matrix substitute ; and with use of radiation therapy in another patient. We did, however, have a second patient who underwent radiation therapy at the site of the wound who healed without complications. In our series, a high number of patients had satisfactory healing.

Limitations of our series relate to the small number of patients with failures. The low number of failures make it difficult to draw conclusions from these outcomes, however, based upon our experiences and review of the literature, failures are associated with infection (*8,9*) and in one case in our series, with use of radiation therapy at the site. It is also possible that unknown or unrecognized sensitivities to the components of the dermal matrix substitute (bovine or shark materials) might be associated with failures, although one of the two patients who failed initially was later treated successfully with the dermal matrix substitute. Patients with exposed bone/muscle/tendon were treated successfully in this series. Each of the patients in this series might have been a candidate for flap coverage ; however, this technique resulted in successful treatment of the wound deficit in most cases without donor site morbidity. This technique is particularly

Table I. — Patient wound details

Patient #	Age	Gender	Location	Wound type	Size (cm)	Exposed tissue	Comorbidities	Complication	% take	# Additional procedures	Additional procedure(s)
1	48	m	dosum hand/ wrist/volar forearm	post infection	10 × 14	tendon	DM	no	100	1	STSG
1	48	m	volar forearm	post infection	10 × 6	tendon	DM	no	100	1	STSG
2	67	f	thumb	resection SCC	2 × 1	tendon/bone	DM	no	100	1	STSG
3	54	m	index finger	trauma	1.5 × 3	tendon/bone	none	no	100	1	STSG
3	54	m	small finger	trauma	1.5 × 2	tendon/bone	none	no	100	1	STSG
4	83	m	dorsal hand	infection	10 × 5	tendon	DM	partial failure	85	0	dressing changes/ vac
5	71	f	dorsal PIP long finger	scleroderma chronic nonhealing wound	1 × 1.5	PIP joint	scleroderma	no	100	0	secondary intent
6	49	f	index middle phalanx (open fracture)	trauma (axe wound)	2 × 2	tendon/bone	none	no	100	0	secondary intent
7	79	m	dorsal hand	trauma (crush)	3 × 3	tendon/bone	coumadin	no	100	1	STSG
8	60	f	thumb (volar)	sarcoma s/p XRT and Wide exc; neurovascular and tendon reconstruction	5 × 4	tendon/nerve/ vessels	XRT	no	100	1	STSG
9	70	m	dorsal-ulnar hand	tumor (subQ lymphoma)	3 × 2	tendon	lymphoma/ chemo	no	100	0	secondary intent
10	73	m	dorsal hand	chemotherapy extravasation	3 × 4	tendon	chemo	no	100	1	STSG
11	14	f	dorsum hand	trauma	4 × 4	tendon, nerve, vessel	none	no	100	1	STSG
11	14	f	volar wrist	trauma	4 × 6	tendon, nerve, vessel	none	no	100	1	STSG
12	43	m	index finger	trauma	2.5 × 7	tendon	none	no	100	1	STSG
12	43	m	long finger	trauma	2.5 × 8	tendon	none	no	100	1	STSG
13	37	m	lower leg	trauma	15 × 12	muscle	none	no	100	1	STSG
14	44	m	hand	parachordoma excisions s/p WLE and brachytherapy	8 × 6	tendon	XRT	severe pain and drainage post STSG (BRACHYTHERAPY) + partial failure integra	10	1	STSG
15	55	m	thumb/hand	trauma	7 × 5	tendon, bone	none	no	100	0	secondary intent
16	32	m	dorsum hand	trauma	5 × 8	tendon	none	no	100	1	stsg

17	21	f	index long and ring fingers	trauma	4 × 2	bone/tendon	none	no	100	1	STSG
18	72	f	TIBIA	osteochondroma	5 × 7	bone	HTN	delayed healing	95	1	stsg
19	28	m	dorsal hand	trauma	7 × 10	bone/tendon	none	no	100	1	stsg
20	32	m	index	trauma	5 × 2	bone tendon	none	no	100	1	FTSG
21	61	m	volar long finger	trauma	2 × 4	tendon	DM/htn	swelling	100	1	STSG
22	23	m	tibia	trauma	5 × 6	bone/muscle	none	no	100	1	STSG
23	29	m	forearm/radial shaft	trauma-gun shot	10 × 5	bone/tendon	none	no	90	1	STSG
24	49	m	dorsal hand	trauma	5 × 4	tendon	none	Venous bleed	95	1	STSG
25	45	m	ulnar forearm	trauma	8 × 15	bone/tendon	none	no	100	2	STSG
26	38	f	volar ring finger	trauma	4 × 2	tendon	none	no	85	1	STSG
27	23	m	dorsal long finger	trauma/heat/crush	3 × 2	bone/tendon	Smoker+ thermal burn	infection & lack of healing	0	3	repeat I&D, rotation flap+ INTEGRA 3 × 2
27	23	m	dorsal ring	trauma/heat/crush	3 × 1.5	bone/tendon	smoker+ thermal burn	infection & lack of healing	0	3	repeat I&D, rotation flap +INTEGRA 3 × 3.2
27	23	m	dorsal small	trauma/heat/crush	3.5 × 2	bone/tendon	smoker+ thermal burn	infection & lack of healing	0	3	free fasciocutaneous flap+ INTEGRA 3 × 3.5
28	85	m	dorsal hand	squamous cell	4.5 × 5	tendon	none	no	100	1	FTSG

DM = diabetes mellitus ; HTN = hypertension ; XRT = radiation therapy ; STSG = split thickness skin graft ; FTSG = full thickness skin graft.

useful in tumor excisions, particularly those in which adequate margins need to be assessed by permanent section. A first stage resection and coverage can be achieved ; margins assessed by permanent pathology, and if needed, additional margins resected at a second date, which typically corresponds to application of a skin graft.

Further large and well-designed prospective series are likely to help determine the limitation and utility of this technique and substance for coverage of challenging wounds.

CONCLUSIONS

Use of a dermal substitute matrix resulted in a high rate of healing of wounds in this series. Further large and well-designed prospective series are likely to help determine the limitation and utility of this technique and substance for coverage of challenging wounds.

Conflict of interest : Julie E. Adams has no conflicts, Marco Rizzo is a consultant for Synthes (no payments) and has a grant pending from SBI and TriMed.

Dr. Capo is a consultant for DePuy Synthes, Wright Medical, and Integra Life Sciences. He has received payment for lectures from Integra Life Sciences.

Ethical statement : All authors (Julie E. Adams, John T. Capo and Marco Rizzo blinded for review) adhere to the ethical standards described by the Committee on Publication Ethics and the International Committee of Medical Journal Editors. The study was completed under an IRB-approved protocol.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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