Title: Utility of Restrata With Split Thickness Skin Graft to Reconstruct the Forearm Donor Site

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Title:
Utility of Restrata with split-thickness skin graft to reconstruct the forearm donor site.

Objective:
Understand association between use of Restrata (Acera Surgical Inc., St. Louis, MO) in forearm flap reconstruction with donor site healing and function.

Hypothesis:
Use of Restrata in combination with split-thickness skin graft for reconstruction of forearm flap reconstruction donor site will be associated with decreased occurrence of tendon exposure at four weeks post-operatively when compared to split-thickness skin graft alone.

Design:
Randomized controlled trial.

Setting:
Single institution, Nebraska Methodist Medical Center

Population:
Adult patients undergoing radial forearm free flap or ulnar forearm free flap at a single institution.

Intervention:
Reconstruction of forearm harvest site using Restrata with a split-thickness skin graft.

Control:
Reconstruction of forearm harvest site using split-thickness skin graft alone.

Inclusion Criteria:
1. All patients age 19 or greater that will undergo radial forearm free flap or ulnar free flap.
2. Photo documentation of wound bed at two weeks and four weeks must be obtainable either by physician or patient.

Exclusion Criteria:
1. Active systemic immunosuppression (active use of high-dose steroids (≥40mg prednisone daily or equivalent) or other immunosuppressive medications OR medical conditions causing immunosuppression, i.e. human immunodeficiency virus etc).
2. Diabetes mellitus with most recent Hemoglobin A1c ≥10.0 within 30 days prior to surgery.
3. Morbid obesity (BMI >40).
4. Inability to maintain wrist immobilization for full planned period.
5. Severe malnutrition (prealbumin levels <10 mg per dL within 30 days prior to surgery OR BMI <15 (very severely underweight).
6. Other conditions felt to significantly impair wound healing per surgeon discretion.

Primary Outcomes:
1. Tendon exposure at four weeks post-operatively (Yes/No).

2. Percentage of surface area of split-thickness skin graft incorporation at four weeks post-operatively.

Secondary Outcomes:
1. Tendon exposure at two weeks post-operatively (Yes/No).
2. Percentage of surface area of split-thickness skin graft incorporation at two weeks post-operatively.
3. Aesthetic appearance of donor site per surgeon rating (graded 1-10).
4. In patients with tendon exposure, time to complete wound epithelialization (measured as time from surgery to first documentation of complete epithelialization in days).
5. Need for re-operation on forearm or secondary wound care strategy after tendon exposure.
6. Forearm infection requiring surgical drainage and/or antibiotics.

Goal Enrollment:
40 total patients with 1:1 group enrollment. Power analysis was performed to identify necessary sample size to detect an absolute reduction of tendon exposure at four weeks of 15% (25% baseline, 10% expected rate with intervention with power of 80% and alpha 0.05). Under these assumptions, 100 patients would need to be recruited into each arm. Recent historical review of institutional volume demonstrates a rate of approximately 35 forearm flaps annually (2019-2020 data). Assuming a 70% study enrollment rate, we would meet enrollment goals in approximately eight years. This time commitment is felt by the study authors to exceed what is reasonable without first generating preliminary data. The proposed sample size is therefore practically derived based annual surgical volume at this institution and available resources from our industry partner. We recognize the limitations in this study, therefore, and that this design is not truly hypothesis testing. Using the above assumptions, we expect goal enrollment to be met within approximately 18 months.

Covariates Recorded:
1. Demographic data - Age, sex, race, ethnicity, BMI.
3. Medical history - Modified frailty index - 5, diabetes mellitus, coronary artery disease, peripheral artery disease, immunosuppression.
4. Social history - Smoking status (current/former/never, total py), alcohol use pattern
5. Wound surface area in square cm.

Randomization:
Occurs when the patient is scheduled for surgery. A simple randomization strategy will be utilized by creating a randomization list using https://www.graphpad.com/quickcalcs/randomize1/, which will ensure equal group distribution. The surgery scheduler will assign patients to their category based on this pre-determined list in consecutive order based on date of surgery scheduling request rather than surgical date to minimize risk of bias.

Consent:
Written informed consent will be obtained at the time of study enrollment and will be stored securely by the Methodist research office. This form is separately attached.

Protocol:

1. All forearm and ulnar flaps will be harvested using a suprafascial harvest technique.
6. Surgical technique for application of Restrata with split-thickness skin graft.
    1. Restrata will be meshed in a 1:2 fashion to allow for egress of serous fluid and minimize risk of fluid collection.
    2. Restrata will be applied to the entire wound bed not amenable to primary closure and will be underlaid beneath the surrounding skin edges.
    3. A split-thickness skin graft is harvested from patient's thigh at 15:1000 inches and placed on top of the Restrata to cover the entire wound bed. The graft is sutured in place using suture choice of surgeon's preference.
    4. Ultrasound gel is applied to the graft and matrix.
    5. Xeroform gauze bolster is placed over the wound and secured using suture choice of surgeon's preference.
    6. The wrist is wrapped with kerlix gauze and the wrist is immobilized
7. Bolsters are removed at five days, the wound is inspected, and high-definition digital photographs are obtained.
8. The arm remains immobilized for two weeks, and daily xeroform dressing changes are performed by patients, family, or home health per treatment team discretion.
9. Immobilizers are removed at initial follow-up visit at two weeks and high-definition digital photographs are obtained. (Any visit between 12 and 16 days will be considered acceptable as two-week follow-up).
10. If graft incorporation is adequate at two-week follow-up per treating physician discretion, Vaseline® or alternative non-antibiotic ointment will be applied to the graft edges between two and four-week follow-up visits by patients, family, or home health per treatment team discretion. If graft failure occurs by two-week follow-up, Aquacel Ag (ConvaTec Medical Group. Deeside, UK) will be applied to the areas of graft failure as the primary treatment strategy with daily dressing changes.
11. High-definition digital photographs are obtained at four-week follow-up.
12. If graft incorporation is adequate at four-week follow-up per treating physician discretion, no additional wound care will be performed. If graft failure occurs by four-week follow-up, Aquacel Ag will be applied to the areas of graft failure as the primary treatment strategy with daily dressing changes.
13. If at any point the treating physician feels that the primary treatment strategy is inadequate or inappropriate, a secondary wound care strategy (alternative treatment, negative pressure therapy, surgical debridement, repeat grafting, etc) may be pursued.
14. In any case of incomplete graft incorporation and/or tendon exposure, further photo documentation will be obtained by the patient, family, or home health or wound team, or physician until epithelialization is complete and further wound care is no longer needed. Details of continued follow-up visits and methods of further documentation will be individualized so as to minimize excessive demands on patient resources.
15. Photos of donor sites at each time period will be submitted for evaluation by two independent surgeons who possess expertise in evaluation of free flap donor site wounds and skin grafts but who will not be involved in enrollment of patients in this trial or of management of their wounds. The percentage of graft incorporation and presence or absence of tendon exposure will be documented by each physician in a blinded fashion. The independent surgeons will also rate donor site graft aesthetic appearance on a 1-10 scale in a blinded fashion. Time to

complete epithelialization will be determined by the treating physician, and photo documentation will be submitted for blinded review by the independent surgeons. Any case of failed epithelialization that does not completely epithelialize within 90 days after surgery will be categorized as “greater than 90 days for analysis”, and all study-related patient contact will cease at that time.

16. Descriptive statistics will be reported. Univariate statistics will be used to compare primary and secondary outcomes between groups.

Premature Termination of Study:
This study may be prematurely terminated by the study team at any point if outcomes appear unequivocally worse than standard of care, if unusual types or rates of complications occur, or if any other safety concerns arise. An interim analysis will be performed in order to assess comparative outcomes following successful treatment of 20 subjects and determine whether to proceed with the remainder of the study.

Variables:

1. Surgical harvest technique will not be standardized between surgeons with the exception of requiring suprafascial harvest overlying the area to be grafted.
2. Donor site of split-thickness graft will be at surgeon discretion.

17. Utilization of purse string suture or other methods to narrow the flap donor site wound prior to grafting.
18. Decision to pursue secondary wound care strategy will be at surgeon discretion, including timing and type of treatment.

Funding Source and Funding Needs:
All Restrata products will be provided at no cost to patients by Acera Surgical Inc. No additional financial resources will be necessary to support this project.

Background Information:
Restrata (Acera Surgical, St. Louis, MO) is a synthetic hybrid-scale fiber matrix that possesses a fibrous structure of varying fiber diameters with high porosity [1]. The architecture of the material, which is similar to native extracellular matrix, allows for cell ingress and retention, as well as neovascularization of newly forming tissue, before completely degrading via hydrolysis [1]. The electrospun matrix is composed of two synthetic biocompatible polymers, polyglactin 910 (PLGA 10:90) and polydioxanone (PDO), both of which are used in other (FDA)-cleared devices, including dura substitutes, resorbable sutures, and orthopedic implants [1]. PLGA 10:90 and PDO were specifically selected in order to achieve a matrix with optimal handling properties and a rate of resorption ideally matched to the process of new tissue formation and wound healing. These polymers are co-electrospun into soft, white, compliant, non-woven sheets capable of supporting the natural wound healing process [1]. Once applied to a wound, the matrix supports cellular infiltration, new tissue formation, and wound healing while progressively resorbing into the tissue over the course of two weeks, on average.

Multiple clinical studies, including retrospective analyses, prospective analyses, and case reports have been conducted to evaluate the clinical efficacy of the synthetic hybrid-scale fiber matrix across multiple use cases in the wound care setting. A summary of the clinical studies and

outcomes can be found in the table below [2-17]. Assessment of over 150 treated wounds of varying etiologies demonstrated that significant wound healing was observed following treatment with the synthetic hybrid-scale fiber matrix across multiple wound types and clinical use settings. Results further demonstrate that the electrospun hybrid-scale fiber matrix also offered unique clinical versatility in facilitating both tissue granulation and a bridge to skin grafting as well as definitive wound closure and re-epithelialization, unlike alternative synthetic scaffolds and matrices.

Published rates of skin graft failure in forearm reconstruction range from 13-38% [18-20]. This occurrence prolongs healing, requires multiple additional health care encounters, and may result in worse aesthetic or event outcomes, sometimes requiring physical therapy. Patients have multiple complex medical needs following head and neck free flap reconstruction, and improving forearm reconstructive outcomes would undoubtedly be beneficial in this setting. Wound care matrices have been investigated in forearm flap reconstruction. Wester et al compared use of STSG alone to the combination of acellular dermal matrix Alloderm (Allergan, Madison, NJ) in combination with STSG [21]. They noted improved cosmesis, similar rates of graft failure, and no cases of secondary graft requirement in the Alloderm + STSG group. Other studies have investigated use of matrices alone or in a staged fashion with grafting [22-25]. Restrata has not previously been studied for this purpose, and in light of the positive outcomes in other similar wounds, investigation of its application to this purpose is relevant.

Clinical indication	# of wounds	Patient demographics	Treatment method	Outcomes	Adverse events	Reference
Chronic wounds (DFUs, VLUs, PUs, traumatic and postsurgical wounds, nonvenous vascular wounds, necrotic wounds)	82	48% male; average patient age 72 years; average wound age 36 weeks; average wound surface area 3.4 cm^2	Multiple applications of the synthetic hybrid-scale fiber matrix as needed for up to 12 weeks	85% complete wound closure at 12 weeks and significant reduction in local inflammation	None	[2]
Recalcitrant neuropathic foot ulcers	4	100% male; patient age range 67-73 years	Weekly, or as appropriate, treatment with synthetic hybrid-scale fiber matrix followed by adjunctive therapy	75% complete wound closure and successful limb preservation	None	[3]
DFUs	24	90% male; average patient age 55 years; average ulcer duration 16 weeks; average ulcer surface area 4.4 cm^2	Weekly, or as appropriate, treatment with synthetic hybrid-scale fiber matrix for up to 12 weeks	75% complete wound closure at 12 weeks	None due to synthetic matrix	[4]

Chronic wounds (DFU, VLU, PUs, Charcot foot deformity)	5	80% male; average patient age 66 years; average ulcer duration 51 months	Multiple applications of the synthetic hybrid-scale fiber matrix as needed in conjunction with NPWT	Formation of granulation tissue, coverage over exposed structures, and reduction in wound size	None	[5]
PUs	11	64% male; average patient age 55 years;	Single application of synthetic hybrid-scale fiber matrix as a foundation for rotational skin flap	Successful granulation tissue formation and preparation of wound site for flap reconstruction, with eventual wound closure rate of 90.9%	None	[6]
Chronic wounds (DFUs, VLUs)	23	60% male; average patient age 68 years; average ulcer duration 16 months	Weekly, or as appropriate, treatment with synthetic hybrid-scale fiber matrix	96% complete wound closure at 21 weeks	None due to synthetic matrix	[7]
TMA wounds	20	85% male; average patient age 62 years	10 wounds treated with synthetic hybrid-scale fiber matrix to augment closure of the suture line and 10 control nonaugmented wounds with standard primary closure	80% complete wound closure following treatment with synthetic matrix; reduced time to healing (18%), compared to control	Wound dehiscence (5), limb loss (2)	[8]
Post-Mohs wounds	10	Patient age range 63-90 years	Multiple applications of the synthetic hybrid-scale fiber matrix as needed	Effective re-epithelialization and wound closure with minimal scarring	Infection (1)	[9]
Post-Mohs wounds	4	75% male; average patient age 78 years; average ulcer surface area 11.5 cm^2	Multiple applications of the synthetic hybrid-scale fiber matrix as needed	100% complete wound closure in 8 weeks with no scars or skin deformities	None	[10]
Peroneal tendon healing	12	25% male; patient age range 18-75 years	Peroneal tendon repair augmented with synthetic hybrid-scale fiber matrix	Significant reduction in pain and rapid return to normal activity	None	[11]
Complex cutaneous wounds (calciphylaxis lesion, abdominal fistula lesion, necrotizing fasciitis lesion)	3	67% male; patient age range 30-54 years	Multiple applications of the synthetic hybrid-scale fiber matrix as needed in conjunction with NPWT	Significant re-epithelialization and healing of the wounds and economic cost savings	None	[12]

Traumatic crush injury wound	1	24-year-old male	Single application of synthetic hybrid-scale fiber matrix as a foundation for STSG	Successful granulation tissue formation and preparation of wound site for STSG	None	[13]
Chronic dorsal foot wound	1	53-year-old male	Multiple applications of the synthetic hybrid-scale fiber matrix as needed	Rapid and sustained coverage of exposed tendons and progressive wound area reduction	None	[14]
DFU	1	66-year-old diabetic male; wound duration >1 year	Multiple applications of the synthetic hybrid-scale fiber matrix as needed	Complete wound closure	None	[15]
Complex lower extremity wounds (scleroderma wound, VLU, amputation wounds)	4	75% male; patient age range 44-74 years	Multiple applications of the synthetic hybrid-scale fiber matrix as needed, in conjunction with HBOT for 2 wounds	75% complete wound closure	None	[16]
Traumatic and thermal burn	1	10-month-old male	Single application of synthetic hybrid-scale fiber matrix	Complete wound closure	None	[17]

DFUs – diabetic foot ulcers; HBOT – hyperbaric oxygen therapy; NPWT – negative pressure wound therapy; PUs – pressure ulcers; STSG – split-thickness skin graft; TMA – transmetatarsal amputation; VLUs – venous leg ulcers.

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