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Maximizing wound coverage in full-thickness skin defects: A randomized-controlled trial of autologous skin cell suspension and widely meshed autograft versus standard autografting

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BACKGROUND: Traumatic insults, infection, and surgical procedures can leave skin defects that are not amenable to primary closure. Split-thickness skin grafting (STSG) is frequently used to achieve closure of these wounds. Although effective, STSG can be associated with donor site morbidity, compounding the burden of illness in patients undergoing soft tissue reconstruction procedures. With an expansion ratio of 1:80, autologous skin cell suspension (ASCS) has been demonstrated to significantly decrease donor skin requirements compared with traditional STSG in burn injuries. We hypothesized that the clinical performance of ASCS would be similar for soft tissue reconstruction of nonburn wounds.

METHODS: A multicenter, within-patient, evaluator-blinded, randomized-controlled trial was conducted of 65 patients with acute, nonthermal, full-thickness skin defects requiring autografting. For each patient, two treatment areas were randomly assigned to concurrently receive a predefined standard-of-care meshed STSG (control) or ASCS + more widely meshed STSG (ASCS+STSG). Coprimary endpoints were noninferiority of ASCS+STSG for complete treatment area closure by Week 8, and superiority for relative reduction in donor skin area.

RESULTS: At 8 weeks, complete closure was observed for 58% of control areas compared with 65% of ASCS+STSG areas ($p = 0.005$), establishing noninferiority of ASCS+STSG. On average, 27.4% less donor skin was required with ASCS+ STSG, establishing superiority over control ($p < 0.001$). Clinical healing (≥95% reepithelialization) was achieved in 87% and 85% of Control and ASCS +STSG areas, respectively, at 8 weeks. The treatment approaches had similar long-term scarring outcomes and safety profiles, with no unanticipated events and no serious ASCS device-related events.

CONCLUSION: ASCS+STSG represents a clinically effective and safe solution to reduce the amount of skin required to achieve definitive closure of full-thickness defects without compromising healing, scarring, or safety outcomes. This can lead to reduced donor site morbidity and potentially decreased cost associated with patient care.Clincaltrials.gov identifier: NCT04091672 (*J Trauma Acute Care Surg.* 2023;96: 85–93. Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level I.

KEY WORDS: Autologous skin cell suspension; soft tissue reconstruction; donor site; necrotizing infection; degloving.

Autografting is the standard of care for treating large skin defects resulting from burns, chronic wounds, trauma, and surgery. Skin autografting requires a secondary wound at the harvest site. Complications associated with the donor site include pain, pruritus, and discomfort, and can be more significant than at the grafted site.[1] Healing at the donor site can be compromised

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by infection, dyschromia, dyspigmentation, and hypertrophic scarring.[1]

Donor skin availability may also be limited for pediatric patients and those with large total body surface area (TBSA) skin defects, while skin quality may be of concern for patients with thin, fragile tissue, or in large areas of previous skin harvest.[1,2] Donor site healing can be prolonged in certain patient populations, such as the elderly, those with diabetes or who are immunocompromised, and individuals with hypermetabolic response to injury.[1,3,4]

The RECELL Autologous Cell Harvesting Device (RECELL® System, AVITA Medical, Valencia, CA) enables point-of-care preparation and spray application of a noncultured autologous skin cell suspension (ASCS) comprised of keratinocytes, fibroblasts, and melanocytes.[5,6] The device was approved by Federal Drug Administration (FDA) for the treatment of burn wounds in 2018, extended to include nonthermal full-thickness skin defects in June 2023. A small piece of the patient's skin is processed, 1 cm^2 of donor skin can be expanded to treat up to 80 cm^2.[6] In acute thermal burn wounds, ASCS has been shown to achieve definitive closure, minimize the donor skin required, reduce donor site pain and scarring, shorten hospital length of stay, and lower costs compared with conventional split-thickness autografting (STSG).[7–12]

Evidence from case studies suggests that ASCS+STSG is effective for the treatment of necrotizing soft tissue infection and other full-thickness skin defects, leading to complete healing, donor skin sparing, and reduced donor site morbidity.[13–16] This study was designed to evaluate the clinical performance of ASCS + widely meshed STSG among patients undergoing reconstruction of full-thickness skin defects not associated with burn injury. It was hypothesized that, compared with treatment with STSG alone, ASCS + more widely meshed STSG would be noninferior for the incidence of complete wound healing at Week 8 and superior in reducing the amount of donor skin required for definitive closure.

METHODS

Study Design

A prospective, multicenter, randomized, evaluator-blinded, 1:1 within-patient controlled trial was conducted at 18 study centers across the United States from February 2020 to 2023 (NCT04091672).[17] The CONSORT 2010 checklist for reporting within-person randomized trials was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content 1, http://links.lww.com/TA/D237).[18]

Patient Eligibility Criteria

Patients 5 years or older requiring autografting for closure of an acute full-thickness nonthermal skin defect were eligible and assessed by the investigator. Included patients had two comparable skin areas ≥80 cm^2 each that required autografting; the maximum area requiring autografting was 50% TBSA. If the defect included the hands, feet, and/or joints, the treatment areas had to be comparable in terms of impacting the same contralateral area.

Patients with the following characteristics were excluded: burn injury at the area requiring autografting, study treatment areas located on face or genitalia, treatment areas that previously failed to heal subsequent to surgical intervention for closure, comorbidities or medication use that could compromise safety or study objectives, and/or a life expectancy <1 year.

Before treatment, each patient underwent a targeted physical assessment. Any changes in physical parameters or health status from the screening assessment were documented. Vital signs and American Society of Anesthesiologists (ASA) Physical Classification score were also recorded.

Wound Bed Preparation

Areas requiring autografting were prepared according to standard practice, including surgical wound bed preparation/excision and hemostasis. If a dermal matrix was previously applied, the matrix had to achieve complete vascularization and cellular ingrowth before autografting.

Study Treatment Area Selection and Randomization

Two comparable contiguous or noncontiguous acute full-thickness skin defect areas of similar size (±20%), defect severity, and prior treatment(s) were identified for each patient in accordance with the study criteria. Each treatment area was marked A or B by the investigator and digital photographs were taken. Treatment areas were randomized using a predetermined random assignment of treatments. An envelope was opened by the investigator to reveal which treatment was assigned to each area. All patients received both study treatments.

Prerandomization Grafting Plan

The investigators prepared an autografting plan consistent with their standard of care that described the STSG meshing size (e.g., 1:1, 1.5:1, 2:1, or 3:1) they would use on the study treatment areas.

Donor Skin Harvesting

Using a dermatome set between 0.006 and 0.012 inch (inclusive), skin for autografting was harvested from a noninjured donor site that had not previously undergone harvesting. Donor skin used for ASCS preparation was harvested at 0.006 to 0.008 inch (inclusive). For each 80 cm^2 of treatment area requiring ASCS (plus any donor site to be treated), 1 cm^2 of skin was harvested. Donor sites harvested for initial treatment and any retreatments were measured and reported as the area of the rectangle encompassing the sites, with digital photographs taken.

Treatment

Treatment types were applied concurrently once wound beds were prepared. For treatment areas randomized to Control STSG, autografting was performed in accordance with the investigator's prespecified graft plan. Treatment areas randomized to ASCS+STSG were treated using the RECELL System (AVITA Medical, Valencia, CA), with ASCS prepared per the product Instructions for Use.[5] ASCS was sprayed over a more widely meshed autograft (i.e., higher meshing ratio) than that noted in the prespecified graft plan (e.g., for a planned 2:1 meshed graft, ASCS +3:1 meshed STSG was used). Meshed autografts were fixed to wounds using surgical glue, suturing, or stapling; fibrin sealant was not permitted. Donor site(s) were treated with ASCS at the investigator's discretion.

The size of each treatment site was measured and reported as the area of the rectangle encompassing each site. Treatment

areas were covered with nonadherent, low-absorbency, small pore, primary dressings (e.g., Telfa Clear Wound Dressing; KPR U.S., LLC); secondary dressings (Xeroform Occlusive Petrolatum Gauze; Covidien) were placed over primary dressings. Additional gauze (for padding) NPWT and crepe bandages were used as needed. Dressings were applied to Control STSG areas before ASCS was applied to ASCS+STSG-assigned areas to avoid overspray on contiguous Control areas. Retreatment or regrafting was performed at the investigator's discretion.

Postoperative Care

Tefla Clear primary dressings remained in place as clinically indicated (typically 6–8 days maximum). Outer and secondary dressings were changed 2 to 3 days posttreatment. Use of silver sulfadiazine, silver-impregnated dressings, and prophylaxis with topical antibiotics was prohibited. In the event of concern for infection, secondary dressings could be replaced with silver-impregnated dressings and microbiological assessments of suspicious areas were conducted.

After healing/closure, treated areas were protected for ≥2 weeks using light (15–20 mm Hg) hydrophobic compression garments/sleeves or dry gauze with secondary dressings as needed and elastic bandaging. Vigorous cleansing and/or excessive application of topical creams was avoided. Thereafter, postoperative care was consistent with the standard of care.

Follow-Up

Each patient participated in up to 11 visits (1 treatment visit and 10 follow-up visits) after initial screening over approximately 52 weeks (±28 days). Visits occurred during Weeks 1, 2, 4, 6, 8, 10, 12, 26, 36, and 52.

Study Endpoints

The primary endpoints were (1) 100% healing (complete closure) of the treatment areas prior to or at 8 weeks after treatment, and (2) comparison of actual expansion ratios for the donor site and treatment areas for each intervention. Healing was defined as the proportion of patients with complete treatment area closure (100% skin reepithelialization without drainage) confirmed at two consecutive study visits at least 2 weeks apart via direct visualization by an evaluator blinded to treatment assignment (i.e., not present for grafting procedure).

Additional endpoints were evaluated. The investigator's unblinded assessment of healing at treatment and donor sites was conducted at all follow-up visits. Blinded treatment site scar outcomes were evaluated at Weeks 26, 36, and 52 by an evaluator and the patient using the Patient and Observer Scar Assessment Scale (POSAS).[19] Skin areas were scored from 1 (normal) to 10 (worst imaginable scar) while considering vascularization, pigmentation, thickness, relief, pliability, surface area, and color. Items in the scales were then summed to produce observer and patient total scores, with higher scores representing worsened scarring.[19] Patient (or parent/guardian) and investigator treatment preferences were assessed at Week 52: everyone was asked whether they were more satisfied with the treatment at area A or B. Patients were asked while blinded to treatment, then again immediately after being unblinded and told how much donor skin was required for each treatment. A post hoc analysis was conducted to evaluate the percentage of patients with ≥95% reepithelialization without drainage confirmed at two study visits, 2 weeks apart, in both treatment areas and according to wound etiology (i.e., traumatic or surgical) ≤8 weeks after treatment.

Safety Assessments

Nonserious adverse events (AEs) and serious adverse events (SAEs) were evaluated within 26 weeks after study treatment. Selected safety events were compared between treatment areas: delayed healing based on investigator's assessment (i.e., treatment areas that did not heal within 8 weeks of the study procedure), incidence of infection, wound durability (based on incidence of recurrent wound breakdown after initial complete closure), scar requiring surgical intervention, and pain (Supplemental Digital Content 2, http://links.lww.com/TA/D239).

Analysis Populations and Statistical Analyses

The planned number of enrolled patients was 65, a sample size deemed adequate to provide ≥80% power for both co-primary endpoints while accounting for missing data and/or a subject attrition rate of approximately 10%. An unblinded conditional power calculation and sample size reestimation was conducted once approximately 50% of total enrollment was completed. Two study populations were considered in the analyses: intention to treat (ITT) and per protocol (PP). The ITT population included all enrolled patients who underwent treatment randomization, with data analyzed based on treatment assigned to an area, regardless of actual treatment. These individuals represented the primary analysis population for evaluation of the superiority hypothesis for donor skin harvesting. The PP population included all ITT patients who received both study treatments and had no major protocol deviations. These patients represented the primary analysis population for evaluation of the noninferiority hypothesis of confirmed healing at ≤8 weeks. All other endpoints were evaluated in the ITT population.

For the co-primary endpoint of healing, noninferiority was evaluated using a 97.5% one-sided confidence interval (CI) for the difference between treatments in the proportion of treatment areas with confirmed healing. Noninferiority of ASCS+STSG to Control STSG was established if the upper limit of the 97.5% CI for the between-treatment difference was <10%. For the co-primary effectiveness endpoint of donor expansion, the actual expansion ratio of the size (area) of donor skin harvested (inclusive of any secondary treatments) to the size of the treatment area was calculated for each treatment received by each patient. A ratio of ratios [R] was then calculated:

$$\frac{\textit{(ASCS ± STSG treatment area/corresponding donor area)}}{\textit{(Control STSG treatment area/corresponding donor area)}}$$

Using these measures eliminates any potential variability from higher meshing ratios with physically lesser expansion at the time of graft placement. The R value was log-transformed for each patient using the natural logarithm (base e) and the mean difference in the log of the R value exponentiated to find the geometric mean ratio (GMR). Superiority of ASCS+STSG over Control STSG was established if the lower limit of the 95% CI for the GMR was >1. This was evaluated using a one-sample t-test at a one-sided 0.025 level of significance. Statistical significance declared if the two-sided p value was <0.05.

For POSAS overall opinion scores, two-sided 95% CIs were presented for the difference in means between treatments at each visit. A paired t-test was used for comparison between treatments. The proportion of subjects/investigators preferring each treatment and corresponding 95% CIs were calculated.

For safety assessments, AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0. Frequencies and percentages of events were summarized overall and for each treatment area by system organ class and preferred term; categorization also occurred by severity and relationship to ASCS. McNemar's Test was used to test for differences between treatments in the incidence of selected AEs of interest.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum, maximum), and categorical variables were summarized using frequencies and percentages.

Ethics

The study protocol, amendments, and informed consent documents were reviewed and approved by the Institutional Review Board (IRB) at each study center prior to study initiation. The study was conducted in accordance with 21 Code of Federal Regulations (CFR) Parts 50 and 312 of the USA, the principles enunciated in the Declaration of Helsinki, and the International Council for Harmonization (ICH) harmonized tripartite guideline regarding Good Clinical Practice. Informed consent was obtained from each enrolled patient in accordance with 21 CFR Parts 50.20–50.27 of the USA.

RESULTS

Patient Demographics and Wound Characteristics

A total of 76 patients consented to the study; after screening, 65 met the eligibility criteria, were randomized to treatment, and comprised the ITT/safety population (Fig. 1). Fifty-two patients received both treatments, had no major protocol deviations, and were included in the PP population. In total, 47 (72.3%) patients completed the study (including all follow-up visits) and 18 (27.7%) patients discontinued.

The mean age was 45.7 years and most patients were male (67.7%) and self-reported as White (70.8%) (Table 1). Fifty-seven patients (87.7%) had ≥1 risk factor for impaired wound healing and most had an ASA score of III (55.4%).

Injury/Defect Types and Characteristics of Treated Areas and Donor Sites

Surgical defects were most commonly due to infection (29 patients [44.6%]), while the most common type of traumatic injury was degloving (15 [23.1%]) (Table 1). Most patients (60 [92.3%]) had received prior treatment for their injuries/defects.

The mean (standard deviation [SD]) percent TBSA affected by injuries or defects was 5.0% (3.9). The mean total estimated area requiring grafting was 757.0 cm^2 (778.9), while the mean total estimated area designated for study treatment was 442.0 cm^2 (380.0) (Table 1). Mean (SD) treatment area sizes were 216.1 (194.7) cm^2 for Control STSG and 211.7 (192.3) cm^2 for ASCS+STSG. Areas treated with ASCS+STSG required less donor skin than Control STSG treatment areas (mean areas for initial treatments: 111.4 cm^2 vs. 157.3 cm^2, respectively). The lower leg was the most frequently treated location. A 2:1 meshing ratio was most common for Control STSG-treated areas (53.8%), while a 3:1 ratio was most common for areas receiving ASCS+STSG (56.9%). Most patients (49 [75.4%]) received concomitant medications, therapies, and/or procedures related to wound healing. The most common concomitant interventions included physical therapy (32 [49.2%]), negative pressure wound therapy (NPWT) (28 [43.1%]), and occupational therapy (12 [18.5%]).

Healing Outcomes

In the PP population, 30 patients (58%) had complete closure at Control STSG areas compared with 34 patients (65%) at ASCS+STSG areas at Week 8 (Fig. 2). The difference in percentages (Control STSG – ASCS+STSG) was −7.0%, with the upper bound of the one-sided 97.5% CI (6.2%; $p = 0.005$) falling within the predefined noninferiority margin (10%), establishing

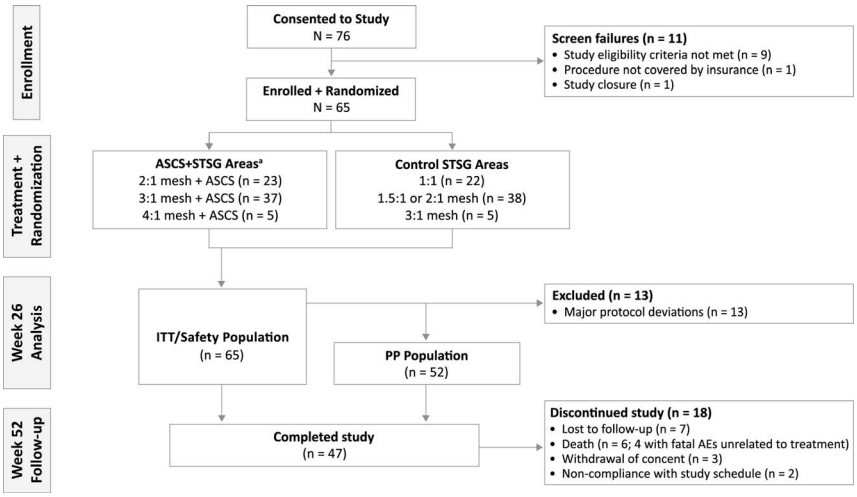

Figure 1. CONSORT diagram. [a]Areas treated with ASCS+STSG received more widely meshed autografts than those indicated in the prespecified graft plan. AE, adverse event; ASCS, autologous skin cell suspension; F/U, follow-up; ITT, intention to treat; PP, per protocol; STSG, split-thickness skin graft.

TABLE 1. Patient, Wound, and Treatment Area Characteristics

Patient Characteristics at Baseline	ITT Population (N = 65)
Sex, male, n (%)	44 (67.7)
Age	
Mean (SD)	45.7 (18.3)
Median (min, max)	46 (15, 85)
Race (patient-reported), n (%)	
White	46 (70.8)
Black or African American	14 (21.5)
American Indian or Alaska Native	2 (3.1)
Hispanic	1 (1.5)
Other	1 (1.5)
Unknown	1 (1.5)
Risk factors for impaired wound healing,* n (%)	
None	8 (12.3)
Obesity	25 (38.5)
Current smoker	22 (33.8)
Diabetes	19 (29.2)
Inadequate nutrition/malnutrition	16 (24.6)
Immunodeficiency	2 (3.1)
Other**	32 (49.2)
ASA physical classification system score, n (%)	
ASA I (normal healthy patient)	5 (7.7)
ASA II (patient with mild systemic disease)	20 (30.8)
ASA III (patient with severe systemic disease)	36 (55.4)
ASA IV (patient with severe systemic disease that is a constant threat to life)	3 (4.6)
ASA V (moribund patient not expected to survive without the operation)	1 (1.5)
Injury/defect type	
Indication for autografting, n (%)	
Surgical etiology	41 (63.1)
Infection, necrotizing	23 (35.4)
Infection, other	6 (9.2)
Fasciotomy/compartment syndrome	5 (7.7)
Other (surgical)	5 (7.7)
Flap donor	2 (3.1)
Traumatic etiology	24 (36.9)
Degloving, open	11 (18.5)
Degloving, closed	4 (6.2)
Crush	3 (4.6)
Traumatic hematoma	2 (3.1)
Road rash	2 (3.1)
Gunshot	1 (1.5)
Laceration	1 (1.5)
Prior treatment	
Debridement	60 (92.3)
Negative pressure wound therapy	55 (84.6)
Dermal substitutes	48 (73.8)
Allografts/xenografts	22 (33.8)
Medications for treatment area	8 (12.3%)
Biological dressings	6 (9.2)
Other interventions	1 (1.5)
Total estimated size of injury/defect, % TBSA	
Mean (SD)	5.0 (3.9)
Median (min, max)	4.0 (1.0, 22.0)
Total estimated area requiring grafting, cm^2	
Mean (SD)	757.0 (778.9)
Median (min, max)	511.0 (160.0, 4,681.0)
Total estimated area designated for study treatment, cm^2	
Mean (SD)	442.0 (380.0)
Median (min, max)	300.0 (85.0, 2,000.0)
Total area of donor skin used to prepare cell suspension for all ASCS-treated areas, cm^2	
Mean (SD), N	8.7 (8.5), 64
Median (min, max)	6.0 (1.0, 48.0)

TABLE 1. *(Continued)*

Treatment Area Characteristics	Control STSG Areas (n = 65)	ASCS + STSG Areas (n = 65)
Size of study treatment area, cm^2		
Mean (SD)	216.1 (194.7)	211.7 (192.3)
Median (min, max)	160.0 (80.0, 1,155.0)	162.0 (80.0, 1,155.0)
Size of donor site for treatment, cm^2		
Mean (SD)	157.3 (121.7)	111.4 (87.5)
Median (min, max)	105.0 (42.5, 660.0)	84.0 (28.0, 460.0)
Treatment area location,† n (%)		
Upper arm	4 (6.2)	4 (6.2)
Lower arm	6 (9.2)	5 (7.7)
Back	3 (4.6)	2 (3.1)
Buttocks	3 (4.6)	2 (3.1)
Upper anterior torso	3 (4.6)	4 (6.2)
Lower anterior torso	6 (9.2)	7 (10.8)
Upper leg	11 (16.9)	11 (16.9)
Lower leg	32 (49.2)	33 (50.8)
Treatment area location included a joint		
Shoulder	0 (0.0)	1 (1.5)
Hip	1 (1.5)	1 (1.5)
Knee	2 (3.1)	2 (3.1)
Meshing ratio used		
1:1	22 (33.8)	0 (0.0)
1.5:1	3 (4.6)	0 (0.0)
2:1	35 (53.8)	23 (35.4)
3:1	5 (7.7)	37 (56.9)
4:1	0 (0.0)	5 (7.7)

*Patients may have had >1 risk for impaired wound healing.
**Examples include substance abuse, peripheral vascular disease, congestive heart failure, and renal impairment.
†Given that some treatment areas covered multiple locations and multiple excision techniques, tools, and graft anchoring types could be used on the same area, values may not sum to the total number of patients.

noninferiority of ASCS+STSG. Results for treatment area closure were similar across study centers and patient subgroups based on age, sex, and race. In unblinded investigator assessments, no significant differences in proportion of treatment area closure were noted between treatment areas at any study visit through Week 52. In the post hoc analysis, the proportion of patients achieving ≥95% healing by Week 8 was comparable between Control STSG and ASCS+STSG areas (87% vs. 85%, respectively; $p = 0.049$) (Fig. 2). Clinical healing between Control

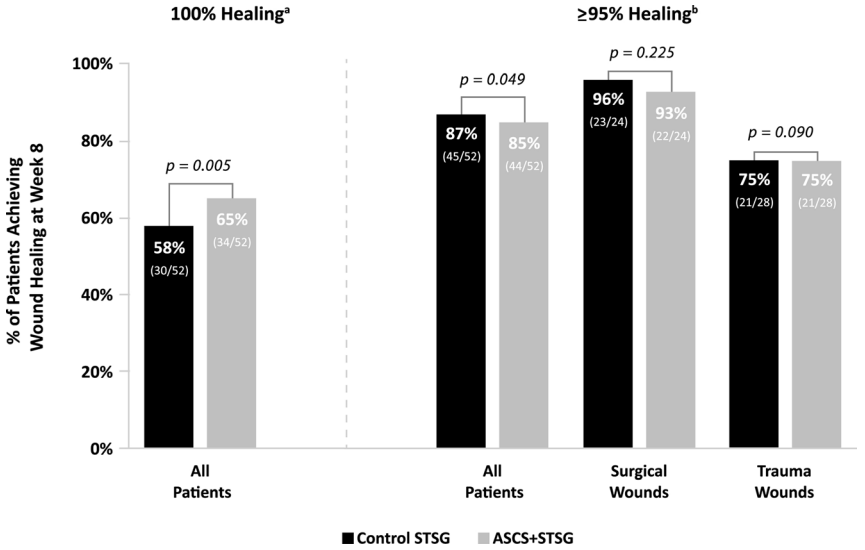

Figure 2. Percentage of patients with 100% and ≥95% wound healing by Week 8. [a]Co-primary endpoint, Control STSG – ASCS+STSG: –7.0% (97.5% CI, 6.2 [upper limit]), $p = 0.005$; non-inferiority of ASCS+STSG established (predefined margin: 10%). [b]Post hoc analysis of ≥95% reepithelialization without drainage confirmed at two visits, 2 weeks apart; analysis for all patients and by wound etiology. ASCS, autologous skin cell suspension; CI, confidence interval; STSG, split-thickness skin graft.

STSG and ASCS+STSG areas remained comparable when analyzed by surgical (96% vs. 93%, respectively; $p = 0.225$) and traumatic (75% vs. 75%, $p = 0.090$) wound etiologies. By Week 2, 83% of all patients with available data (34/41) showed ≥95% reepithelialization of donor sites.

Donor Skin Expansion

Similar treatment area sizes were evaluated for the Control STSG and ASCS+STSG groups (Table 1; Fig. 3A). However, more donor skin was required for treatment of Control STSG areas than ASCS+STSG areas (mean [SD]: 157.3 [121.7] cm^2 vs. 111.4 [87.5] cm^2, respectively), reflecting a 27% reduction with ASCS+STSG. The mean (SD) actual expansion ratios (i.e., treatment area size/corresponding donor site area size) were 1.40 (0.43) for Control STSG and 1.84 (0.48) for ASCS+STSG treatment areas (Fig. 3B). The GMR of the actual expansion ratios was 1.33 (95% CI, 1.24–1.42; $p < 0.001$). Given the lower limit of the 95% CI for GMR was >1, superiority of ASCS+STSG over Control STSG for relative reduction of donor skin use was established. Similar results were observed across study centers and across patient subgroups based on age, sex, and race.

Scar Outcomes

No significant and clinically meaningful differences between treatment areas were observed on the POSAS observer and patient scores (including total and overall opinion scores) for long-term wound appearance (see Supplemental Digital Content 3, http://links.lww.com/TA/D238).

Patient and Investigator Treatment Preferences

At Week 52, 18 of 47 patients (40.0%; 95% CI, 25.7–55.7) preferred the ASCS-treated area, with no meaningful difference between blinded and unblinded assessments. Among the investigators, 18 of 47 (40%; 95% CI, 25.7–55.7) preferred the ASCS-treated area.

Safety Analyses

Forty-two patients (64.6%) experienced a total of 161 nonserious AEs, and 26 patients (40.0%) experienced a total of 50 SAEs. The Control STSG and ASCS+STSG approaches had similar safety

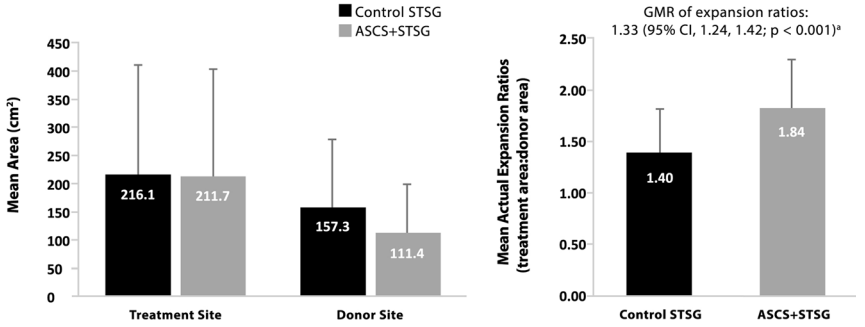

Figure 3. Comparison of (*A*) treatment and donor site areas and (*B*) expansion ratios. Data plotted as mean and error bars indicate standard deviations. [a]Superiority of ASCS + STSG established, given GMR >1. ASCS, autologous skin cell suspension; CI, confidence interval; GMR, geometric mean ratio; STSG, split-thickness skin graft.

profiles, with no unanticipated events. Twenty-four (36.9%) subjects reported AEs of interest at the RECELL and/or Control treatment areas (Supplemental Digital Content 3, http://links.lww.com/TA/D238). Between-treatment differences in delayed healing and wound durability issues were not significant (p = 1.00). Other AEs of interest were either not reported or not reported at Control STSG and/or ASCS+STSG treatment areas. Three patients (4.6%) experienced events that were possibly device-related, all of which were nonserious and resolved (1 with medication and 2 on their own). These events included one case of 1% excessive granulation tissue and two cases of impaired healing; delayed healing was also reported in the Control STSG areas for these two cases. Three patients had treatment areas that received autograft retreatment: two patients at both study areas, and one patient at their Control STSG area. No retreatments used the ASCS device. Three patients died in association with an SAE during the study; no fatal SAE was related to study treatment.

Representative Case Example 1

A 20-year-old male sustained a 4% TBSA open degloving injury of the lower leg (Fig. 4). Treatment area sizes were 182 cm^2 for Area A (Control STSG, 2:1 mesh) and 162 cm^2 for Area B (ASCS+STSG, 3:1 mesh); donor site sizes were 130 cm^2 and 100 cm^2 for these areas, respectively. At ≤8 weeks after treatment, 100% healing was observed at the ASCS+STSG-treated area but not the Control STSG area.

Representative Case Example 2

A 32-year-old male presented with a 13% TBSA necrotizing infection of the lower anterior torso (Fig. 5). Treatment area sizes were 555 cm^2 for Area A (Control STSG, 2:1 mesh) and 544 cm^2 for Area B (ASCS+STSG, 3:1 mesh); donor site sizes were 222 cm^2 and 198 cm^2 for these respective areas. At ≤8 weeks after treatment, 100% healing was observed at the ASCS+STSG-treated area but not the Control STSG area.

DISCUSSION

This study is the first randomized clinical trial to evaluate the safety and effectiveness of ASCS used in combination with widely meshed STSG for the treatment of patients with full-thickness nonthermal skin defects. Both primary endpoints were met, with ASCS+STSG showing noninferiority for complete healing by Week 8 (65% vs. 58% with Control STSG) and superiority for donor skin expansion compared with Control STSG. Approximately 27% less donor skin was required for use of ASCS +STSG compared with Control STSG, an observation aligned with the donor skin-sparing benefits of ASCS reported in clinical studies of patients with full-thickness thermal burn injuries.[7–9] Evaluation of ≥95% healing at Week 8, an outcome regarded by some experts to have greater clinical relevance than complete closure, showed that the incidence of healing was comparable between Control STSG and ASCS+STSG areas (87% vs. 85%) regardless of wound etiology. The incidence of ≥95% reepithelization among treatment groups was lower for traumatic etiologies (75% vs. 75%) than surgical etiologies (96% vs. 93%). This finding may be attributed to the increased risk of microvascular injury, wound depth, and degree of wound contamination associated with traumatic injury.

NPWT is used by many to bolster dressing over STSGs. NPWT was used as pretreatment and or as a bolster (27 patients) and employed equally for both treatment and control sites. Results therefore include the effect of NPWT in both areas. To our knowledge, there is one meta-analysis that concludes NPWT increases graft take by 7%.[20] No studies have indicated decreased time to healing. The focus of this study was to demonstrate noninferiority in wound healing between standard and ASCS + STSG. Future studies could include a study arm utilizing NPWT to secure STSGs to examine the impact if any on time to healing.

Blinded observer and patient assessments of treatment area scarring using the POSAS indicated that the benefits of ASCS+STSG were achieved without increasing scar scores. Evaluation of treatment preferences suggested that 40% of unblinded patients and investigators were more satisfied with ASCS+STSG-treated areas than Control STSG at Week 52, with CIs including 50%. No detailed information was recorded indicating why one treatment was selected over another, and preference could be related to several factors including wound bed preparation, graft placement, meshing ratio, and/or not having the option to answer, "no preference." Finally, the observed safety profile

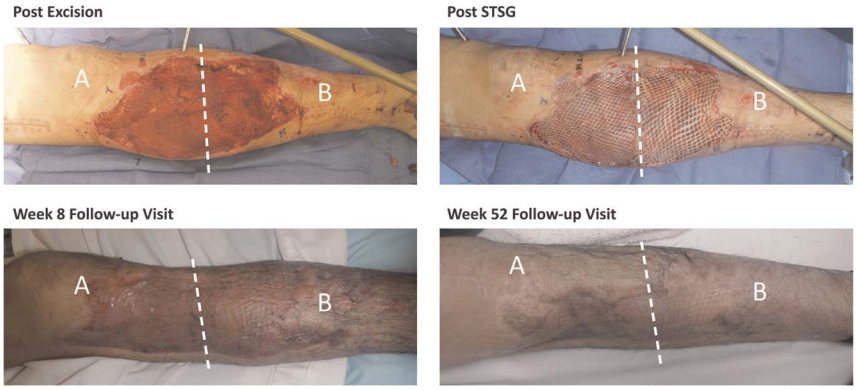

Figure 4. Representative case example 1. 20-year-old male with 4% TBSA open degloving injury of the lower leg. Risk factor for impaired wound healing: vascular injury. Prior treatments: muscle flap and NPWT. Total area requiring grafting: 550 cm^2; total treatment area: 344 cm^2. Area A (182 cm^2) treated with Control STSG (2:1 mesh), Area B (162 cm^2) treated with ASCS+STSG (3:1 mesh). Donor site sizes were 130 cm^2 and 100 cm^2, respectively, a 23% reduction of donor skin with ASCS+STSG. See text for additional details. ASCS, autologous skin cell suspension; NPWT, negative-pressure wound therapy; STSG, split-thickness skin graft; TBSA, total body surface area.

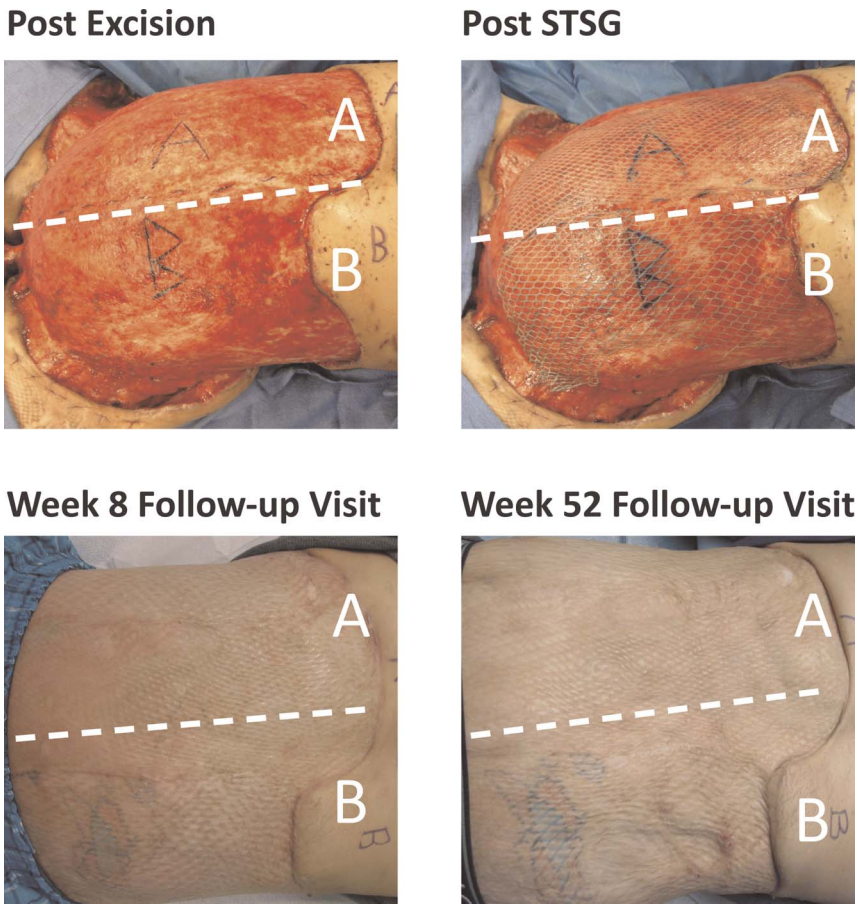

Figure 5. Representative case example 2. 32-year-old male with a 13% TBSA necrotizing infection of the lower anterior torso. Risk factors for impaired wound healing: current smoker, paraplegia. Prior treatments: allografting/xenografting. Total area requiring grafting: 4,681 cm^2; total treatment area: 1,099 cm^2. Area A (555 cm^2) treated with Control STSG (2:1 mesh), Area B (544 cm^2) treated with ASCS+STSG (3:1 mesh). Donor site sizes were 222 cm^2 and 198 cm^2, an 11% reduction of donor skin with ASCS+STSG. See text for additional details.ASCS, autologous skin cell suspension; STSG, split-thickness skin graft; TBSA, total body surface area.

was similar between approaches, including for key AEs of interest such as delayed healing, infection, and wound durability.

Although it remains to be evaluated in this patient population, the reduced donor skin requirements associated with ASCS +STSG may improve healthcare utilization through reductions in time to healing, the number of surgical procedures required for wound closure, donor site complication management, operating room time, length of stay, and overall costs. The economic benefits associated with donor site sparing are most obvious in patients with larger wounds. For patients with smaller wounds, having a smaller donor site without a substantial increase in healing time may offer other benefits that are less easily measured in terms of pain, requirements for wound care, and return to function. Many of these clinical and economic benefits have already been observed with use of ASCS±STSG in the treatment of acute thermal burn injuries with sizes up to 49% TBSA.[7,9–12]

A strength of the current study includes incorporation of a within-patient control design, resulting in closely matched wound areas that permitted rigorous comparison of the effects of each treatment approach. Patient-reported outcomes, a critical consideration given the impact of reconstruction outcomes and scarring on psychosocial well-being,[21,22] were assessed using a standardized and validated tool, the POSAS. However, some limitations should be noted. Firstly, the other patient-reported outcome included in this study, treatment preference, was not measured using a validated tool, as one is not available. Without additional qualitative measures to provide context, the subjective responses could not be appropriately interpreted to better understand what led to the preference of one treatment over another. Secondly, as the study primarily included White male patients with ≥1 risk factor for impaired healing, it may be inappropriate to generalize the results to patients of other ethnicities, female sex, and risk levels for healing. In addition, direct comparison of healing outcomes using a standard meshed autograft with and without ASCS was not performed, as the purpose was to evaluate whether donor skin size could be reduced. However, preclinical evidence suggests that improved time to reepithelization can occur when comparing the same size meshed autograft with and without ASCS.[23]

In summary, the results of this randomized clinical trial show that the significant donor skin-sparing benefits of ASCS +STSG observed in thermal burn injuries extend to the reconstruction of full-thickness traumatic and surgical skin defects. ASCS+STSG presents a novel strategy for surgeons performing such procedures, and results in healing comparable to lower

meshed ratio grafting without ASCS. These findings indicate that ASCS+STSG is an effective autograft-sparing technology that may offset some of the morbidity associated with donor sites. This approach may be especially beneficial for patients with limited availability and/or usability of donor skin, such as children and those with large injuries.[2,24] Similarly, patients with risk factors for impaired healing and risk of hypertrophic scarring may also derive particular benefit. Ongoing evaluations will confirm whether the healthcare resource utilization benefits observed in burn care with ASCS will translate to this population.

AUTHORSHIP

SH advised on the study and contributed to the critical revision of the manuscript. All other authors contributed to data collection and critical revision of the manuscript.

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DISCLOSURE

M.G. is a consultant for AVITA Medical. K.N.F. has completed multiple research projects and is a consultant for AVITA Medical. H.P. is a consultant for AVITA Medical and Spectral MD. J.S. is a consultant for AVITA Medical and Mallinckrodt, and has received research funding from Mallinckrodt, AVITA Medical, Polynovo, Skingenix, Takeda, Mediwound, Spectral MD, Syndgen, Uluru, Philips, Asell, Urgo Medical, and Organogenesis. N.M. is a consultant for AVITA Medical. H.M. is a consultant for AVITA Medical and Keracis. A.C. is a consultant for AVITA Medical. L.C. is a consultant for AVITA Medical and Smith and Nephew. D.B. and J.A.M. have been consultants for AVITA Medical. Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D336).

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