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# Prospective Randomized Trial of Accelerated Re-epithelization of Skin Graft Donor Sites Using Extracorporeal Shock Wave Therapy

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- BACKGROUND:** Extracorporeal shock wave therapy may enhance revascularization and repair of healing soft tissue.
- METHODS:** Between January 2006, and September 2007, 28 patients with acute traumatic wounds and burns requiring skin grafting were randomly assigned in a 1:1 fashion to receive standard topical therapy (nonadherent silicone mesh [Mepitel, Mölnlycke Health Care] and antiseptic gel [polyhexanide/octenidine]) to graft donor sites with (n = 13) or without (n = 15) defocused extracorporeal shock wave therapy (ESWT, 100 impulses/cm<sup>2</sup> at 0.1 mJ/mm<sup>2</sup>) applied once to the donor site, immediately after skin harvest. The randomization sequence was computer generated, and the patients were blinded to treatment allocation. The primary endpoint was time to complete donor site epithelialization and was determined by an independent blinded observer.
- RESULTS:** Statistical tests indicated no unbalanced distribution of subject characteristics across the two study groups. Mean times to complete graft donor site epithelialization for patients who did and did not undergo ESWT were 13.9 ± 2.0 days and 16.7 ± 2.0 days, respectively (p = 0.0001).
- CONCLUSIONS:** For centers that apply nonadherent gauze dressings and topical antiseptics to skin graft donor sites, application of a single defocused shock wave treatment immediately after skin graft harvest can significantly accelerate donor site epithelialization. (J Am Coll Surg 2010;211:361–367. © 2010 by the American College of Surgeons)
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The split thickness skin graft (STSG) remains a proven and reliable means of establishing definitive coverage of wounds that cannot be approximated primarily. STSG incorporation and survival in the recipient wound bed relies principally on angiogenesis. The graft donor site typically re-epithelializes within 10 to 15 days. However, the considerable degree of donor site pain, associated reduction in quality of life, and suboptimal cosmetic appearance during

this period of healing, leave donor site healing and morbidity an unsolved problem in surgery. The numerous existing approaches to donor site management suggest that no single method has proven perfectly suitable. Nonetheless, treatments capable of accelerating keratinocyte proliferation and angiogenesis at the donor site and of providing effective relief of pain and distress remain the focus of active clinical investigation.

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Therapeutic strategies aimed at promoting tissue repair in open wounds have emphasized the stimulatory effects of mechanotransduction.<sup>1,2</sup> One such modality is microdeformational wound therapy using vacuum-assisted closure to promote neovascularization, granulation tissue formation, and epithelial cell proliferation within the open wound.<sup>3,4</sup> Innovative approaches to accelerate wound healing and tissue regeneration have broadened the potential clinical utility of other noninvasive biomechanical therapeutic modalities.<sup>5-7</sup> A modality that has shown promise as a wound healing adjunct is extracorporeal shock wave therapy (ESWT).

Recent mechanistic studies of ESWT have demonstrated proangiogenic and anti-inflammatory responses in ischemic skin flaps and acute burns in animal models; however, the mechanisms responsible for the favorable biologic response to shock waves in humans remain to be established.<sup>8-12</sup> Our phase II clinical trial has shown low-energy, unfocused ESWT to be feasible and well tolerated by patients with complicated, nonhealing acute and chronic wounds and burns.<sup>7</sup> Having shown that shock waves applied immediately after skin transplantation stimulate proangiogenic gene expression and suppress local inflammatory responses in animals,<sup>12</sup> and having demonstrated the potential for therapeutic shock waves to accelerate wound repair and re-epithelialization with a favorable therapeutic (risk/benefit) ratio in humans,<sup>7</sup> we undertook this prospective randomized trial to determine if the noninvasive application of shock waves are beneficial in improving donor site outcomes through accelerated re-epithelialization.

## METHODS

This report complies with the reporting standards established by the revised Consolidated Standards of Reporting Trials (CONSORT) consensus statement.<sup>13</sup>

### Participants

A prospective randomized clinical trial was conducted from January 2006 to September 2007, and was approved by the Charité Berlin Ethics Committee, under authorization number EA/160/06. During the study period, 28 patients enrolled and provided informed consent. Once eligibility was confirmed, study subjects were assigned randomly to one of two study groups, one undergoing either daily STSG donor site dressing changes with application of topical nonadherent silicone mesh (Mepitel [Mölnlycke Health Care]) and antiseptic gel (polyhexanide/octenidine), according to institutional standards of practice, the other undergoing the same topical therapy in addition to unfocused shock wave therapy.

Eligible patients were men or nonpregnant women, between 18 and 80 years of age, capable of providing informed consent. Eligible patients required skin grafting but did not have insulin-requiring diabetes mellitus, dialysis-dependent renal failure, ongoing systemic therapy for malignancy, systemic dermatologic disease, ongoing corticosteroid therapy, or active drug abuse. None of the 28 study subjects enrolled were excluded from the study, so there were 28 evaluable patients who were blinded to treatment allocation.

### Shock wave administration

After STSG excision (minimum size 10 × 20 cm) with a battery or compressed air-powered dermatome at a thickness of 2 mm, unfocused shock wave therapy was administered to the donor site of study subjects randomized to the ESWT intervention arm of the study. The shock waves were delivered to the donor site intraoperatively on the anesthetized study subject, as a single treatment immediately after STSG harvest. On average, treatment time was 13 minutes. The administered shock wave dose was 100 impulses/cm<sup>2</sup> (according to donor site surface area) using an energy flux density of 0.1 mJ/mm<sup>2</sup>. Based on our previous clinical experience treating acute and chronic soft tissue wounds and burns,<sup>7</sup> we elected to use the average energy flux density (0.1 mJ/mm<sup>2</sup>) typically applied for these indications in the range of 0.03 to 0.15 mJ/mm<sup>2</sup>. This energy flux density represented the threshold for biologic response of the target tissue, which was defined in our laboratory animal models.<sup>11,12</sup> Our previous laboratory animal dose response experiments indicated that 100 pulses/cm<sup>2</sup> was the optimal dose for the indications in this study.

Sterile ultrasound conducting gel (Lavasept Gel, prepared using concentrated Lavasept, Fresenius, Bad Homburg, Germany) was applied to the donor site wound surface. To allow good coupling conditions, a sterile plastic protective film was placed over the wound. Ultrasound gel was then applied onto the drape as a coupling media. Unfocused shock waves were applied through the conducting gel and sterile film directly to the donor site, using the OW180C DermaGold (MTS Europe GmbH, a subsidiary of Tissue Regeneration Technologies, LLC), which is a certified medical device in Europe (TÜV Rheinland CE 1275). The parabolic reflector used in the therapy head of the OW180C DermaGold allows the shock waves to be unfocused, allowing a large target treatment area to be stimulated by the acoustical field. After STSG (and completion of ESWT in the intervention arm), all study subject donor sites were covered with topical nonadherent silicone mesh (Mepitel) and antiseptic gel (polyhexanide/octenidine), which were replaced daily until complete re-epithelialization.

### Primary outcomes (donor site epithelialization) assessment

Study participants who provided informed consent to participate in this clinical trial were followed in-hospital daily for a period of 11 to 21 days (median 15 days) and were evaluated 12 weeks after hospital discharge in an outpatient clinic. After STSG harvest and during each visit, computerized digital management planimetry was used to define the extent of donor site surface area re-epithelialization. This software provides an objective method for accurate wound surface measurements through calibrated digital images. It automatically provides the length, width, and surface area of the digitally imaged donor site. Complete donor site healing was defined as  $\geq 95\%$  re-epithelialization. Study subjects were monitored carefully during the follow-up period for cardiac, neurologic, dermal, thermal, or allergic reactions or adverse events.

### Objective

The principal aim of this study was to determine if a single application of defocused ESWT to the donor site immediately after STSG can accelerate re-epithelialization over our current standard of practice. The null hypothesis tested ( $H_0$ ) in this study was that there is no difference in time to complete donor site re-epithelialization between our institutional standard of practice for topical donor site care, and ESWT combined with our standard care for patients undergoing split thickness skin grafting. The alternate hypothesis ( $H_1$ ) is that there is a standard deviation difference of 2 days in time to epithelialization between our standard of practice for topical donor site care and standard of practice and ESWT.

### Outcomes

The primary outcomes variable was time to complete donor site healing ( $\geq 95\%$  re-epithelialization).

### Sample size

Sample size calculation was based on the assumption that mean time to epithelialization for the control wound will be 17 days (range 13 to 20 days). The estimated standard deviation (SD) for the differences in time to epithelialization is assumed to be 2 days. Controlling for the probability of a type I error at  $\alpha = 0.01$  (to allow for comparison of up to 5 outcomes variables, the type I error has been reduced from 0.05 to 0.01 using a Bonferroni correction [ $0.05/5 = 0.01$ ]), a total study sample size of 27 subjects per group would have 80% power to detect a difference of 2 days in time to healing between shock wave treated and control donor sites.

### Randomization

Subjects were randomized in a 1:1 ratio to undergo either application of topical nonadherent silicone mesh (Mepitel)

and antiseptic gel (polyhexanide/octenidine) beginning immediately after STSG harvest and changed daily, or a single, unfocused shock wave treatment at 100 impulses/cm<sup>2</sup> and 0.1 mJ/mm<sup>2</sup> immediately after STSG harvest, which was followed by application of topical nonadherent silicone mesh (Mepitel) and antiseptic gel (polyhexanide/octenidine), changed daily. Randomization was achieved through a computerized randomization system (without stratification) based on random number generation at the Unfallkrankenhaus Berlin, Zentrum für Schwerbrandverletzte mit Plastischer Chirurgie. The randomization sequence was concealed until the treatment group was assigned. The study participants were blinded to group assignment; the primary endpoint, time to complete donor site epithelialization, was determined by independent, blinded, observer. Serial digital images of all study subject donor sites were reviewed by an expert in wound care who was blinded to treatment group assignment, and who determined completeness of donor site epithelialization.

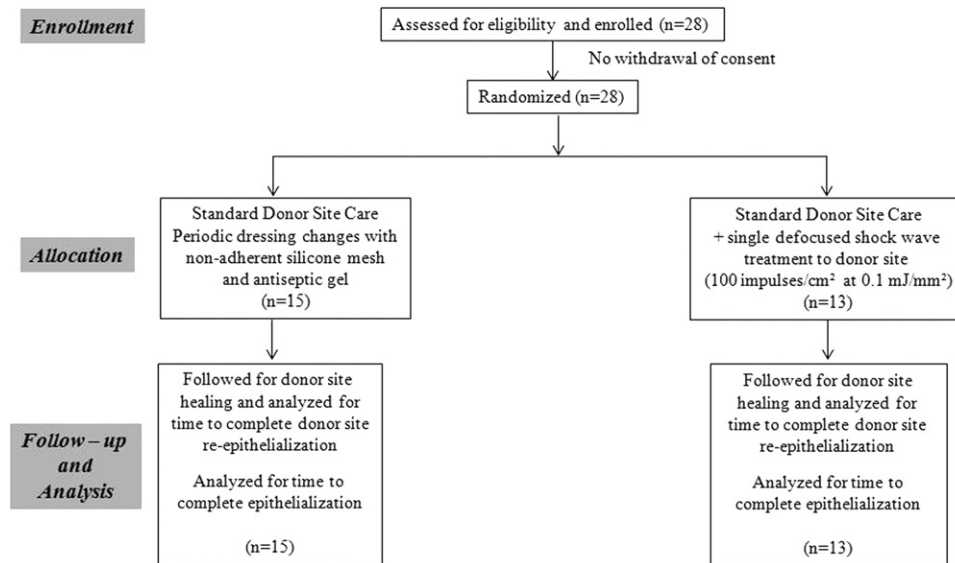
### Statistical methods

Summary statistics were obtained using established methods. The categorical variables between groups were compared using Fisher exact test or chi-square test, as appropriate. Continuous data are presented as means and standard deviations (mean  $\pm$  SD) and were compared using the 2-sample *t*-test to adjust for potentially important clinical/pathologic factors. If assumptions for normality were not satisfied (determined by the Shapiro-Wilk test), then data were summarized using the median and range, and groups were compared using the Wilcoxon rank sum test. The primary outcomes variable in this study was time to donor site re-epithelialization, which was defined as time from STSG harvest to the first documentation of complete donor site healing ( $\geq 95\%$  re-epithelialization). Mean time to donor site epithelialization ( $\pm$  SD) was compared between study groups with analysis of variance. Statistical analysis was performed using JMP(v8) and SAS software (JMP and SAS). A *p* value  $< 0.05$  was considered significant. Interim primary outcomes analysis was planned midway through the study at approximately 50% target accrual.

## RESULTS

### Patients

From January 2006 to September 2007, 28 patients were assessed for eligibility, and all provided consent to participate and enrolled in the study (Fig. 1). These patients were randomized into one of two groups: institutional standard of practice for donor site wound care with ( $n = 13$ ) or



**Figure 1.** Flow of participants through each stage of the trial.

without ( $n = 15$ ) ESWT. All 28 subjects were available for final analysis. Baseline demographic characteristics of the study participants are reported in Table 1. Subjects were predominantly healthy middle aged males, mean age  $48.8 \pm$

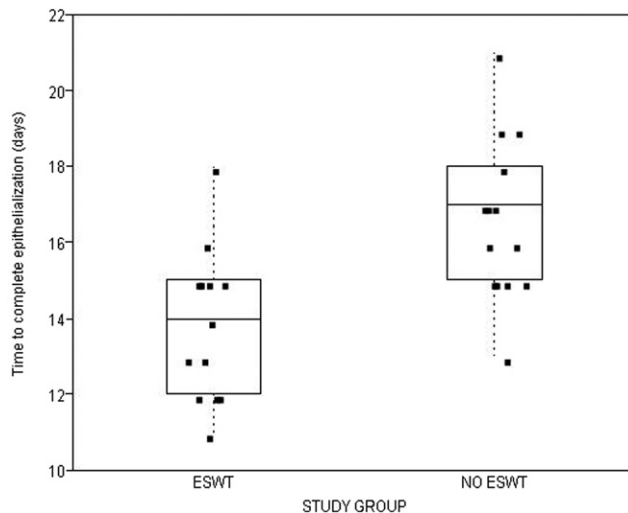
15.5 years. The principal indication for STSG was coverage after burn wound excision. Statistical tests indicated no unbalanced distribution ( $p > 0.05$  for all comparisons) of study subject characteristics across the two study groups.

**Table 1.** Distribution of Subject Characteristics Across the Two Study Groups

Characteristic	Study group				p Value	Total patients	
	Standard (n = 15)		ESWT (n = 13)			n	%
	n	%	n	%			
Gender					0.83		
Female	4	26.7	3	23.1		7	25.0
Male	11	73.3	10	76.9		21	75.0
Age (y), mean $\pm$ SD	45.9 $\pm$ 18.4		52.1 $\pm$ 11.1		0.30	48.8 $\pm$ 15.5	
Diabetes mellitus, noninsulin requiring	0	0	0	0	1.00	0	0.0
Cardiac or peripheral vascular disease	2	13.3	3	23.1	0.88	5	17.9
Immunosuppression (eg, HIV, AIDS)	0	0	2	15.3	0.48	2	7.1
TBSA burn (%), median (range)	3 (1–22)		4 (1–36)		0.69	4 (1–36)	
Traumatic injury category					0.67		
Wound	3	25.0	4	30.8		7	25.0
Burn	12	80.0	9	69.2		21	75.0
Postinjury hypoxemia or hypotension	1	6.7	0	0	1.00	1	3.6
Inhalational injury	1	6.7	0	0	1.00	1	3.6
Need for mechanical ventilation	2	13.3	0	0	0.48	2	7.1
ICU care	3	20.0	3	23.1	1.00	6	21.4
ICU length of stay (d), median (range)	0 (0–25)		0 (0–14)		0.92	0 (0–25)	
Blood product transfusion	1	6.7	1	7.7	1.00	2	7.1
Hospital-acquired infection	2	13.3	3	23.1	0.64	5	17.9
Postinjury bacteremia	2	13.3	3	23.1	0.64	5	17.9
Wound interventions, mean $\pm$ SD*	3.3 $\pm$ 1.1		4.5 $\pm$ 2.7		0.35	3.8 $\pm$ 2.0	

\*Refers to interventions unrelated to the donor site, rather the recipient wound for split thickness skin graft. ESWT, extracorporeal shock wave therapy; TBSA, total body surface area.





**Figure 2.** Time to complete epithelialization in patients with and without single postharvest defocused shock wave treatment to the donor site. ESWT, extracorporeal shock wave therapy.

### Toxicities

There were no reported cardiac, neurologic, dermal, thermal, or allergic reactions or adverse events. No clinically apparent infection, bleeding, swelling, or adverse skin reaction developed at donor sites treated with or without shock waves.

### Donor site re-epithelialization

All donor sites healed over a range of 11 to 20 days. Mean times to complete graft donor site epithelialization for patients who did and did not undergo ESWT were  $13.9 \pm 2.0$  and  $16.7 \pm 2.0$  days, respectively (Fig. 2;  $p = 0.0001$ ). So, the significantly faster donor site epithelialization evident in the shock wave treated group than the control group, at time of interim analysis, prompted early study termination.

### DISCUSSION

The STSG is commonly used by surgeons worldwide for a variety of indications including burns, soft tissue wounds, and the open abdomen. Despite its widespread use, few studies have been completed using investigational wound healing modalities showing a significant benefit in time to re-epithelialization of STSG donor sites.<sup>14</sup> This prospective randomized trial evaluated the efficacy of a single unfocused shock wave application immediately after STSG harvest as a means to accelerate donor site re-epithelialization. Patients receiving shock wave therapy (100 impulses/cm<sup>2</sup> at 0.1 mJ/mm<sup>2</sup>) showed significantly reduced time to complete donor site wound healing ( $13.9 \pm 2.0$  days vs  $16.7 \pm$

2.0 days) compared with our institutional standard of practice alone (nonadherent silicone mesh [Mepitel] and antiseptic gel [polyhexanide/octenidine]). During a 3-month follow-up period, there was no treatment-related toxicity, infection, or deterioration of ESWT-treated donor site wounds. The statistically significant increase in rate of donor site re-epithelialization observed in the intervention arm of the study prompted early termination of this clinical trial.

Many wound care strategies are used in the management of STSG donor sites. A detailed review of these numerous treatment options is beyond the scope of this article, but a brief review is warranted. The option used as the control in this study was a nonadherent silicone mesh (Mepitel) and antiseptic gel (polyhexanide/octenidine). Rennekampff and colleagues<sup>14</sup> studied many of the other commonly used dressings to include petroleum gauze, a biosynthetic wound dressing (Biobrane, Smith & Nephew), an occlusive film dressing (Barrier Flex, Mölnlycke Health Care GmbH), and an equine collagen foil (Tissu Foil E, Baxter). Options in wound dressing management exist in addition to the many dressing types. For example, some surgeons opt to use heat lamps in addition to the dressing, while others do not. Although many of these dressings have been compared in randomized double-blinded studies, no donor site wound treatment algorithm has been shown to be decidedly superior.

Shock wave therapy is an existing technology that has been used in a variety of disease processes including nephrolithiasis and numerous orthopaedic indications. In the last decade it has been increasingly studied in the wound healing arena. Preclinical and clinical studies have shown ESWT to limit deleterious proinflammatory effects inhibiting wound healing, to have antimicrobial properties, to enhance tissue oxygenation and fibroblast recruitment, and to improve neoangiogenesis of healing tissue.<sup>9,11,15</sup> Although this study represents the first prospective randomized use of ESWT in STSG donor sites, a body of literature exists showing the benefit of ESWT in wound healing. This modality has been investigated in a variety of traditionally problematic soft tissue wounds including diabetic foot ulcers,<sup>16</sup> burns,<sup>17</sup> and chronic decubitus ulcers.<sup>18</sup> Most studies have used ESWT in the operative or postoperative setting, but even the preoperative use of ESWT in planned tissue flaps has significantly increased flap viability in preclinical studies.<sup>19</sup> No serum or wound fluid inflammatory markers were analyzed in this trial to assess for local or systemic cytokine or chemokine response, but we suspect that the benefit seen in ESWT-treated STSG donor sites was also likely due to the anti-inflammatory and proangiogenic properties of

ESWT treatment, coupled with ESWT-augmented growth factor release and fibroblast recruitment.

Despite the advantages demonstrated in more rapid time to epithelialization when a single ESWT is administered immediately after STSG harvest to the donor site, followed by our institutional standard of donor site management, this study has limitations. In our original power analysis indicating the need for 27 subjects per group, we allowed for comparison of both our primary endpoint and for up to 5 secondary endpoints. This study was terminated early, with only 13 and 15 patients in the ESWT and non-ESWT groups, respectively, due to the significant difference seen in time to re-epithelialization observed at time of planned interim analysis. Because of these limited sample sizes, our study is underpowered to allow for comparison of other parameters of interest. In addition, this particular study did not address other outcomes variables relevant to this patient population, namely pain, symptom distress, quality of life, cosmesis of donor sites, or long-term follow-up. In addition, the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE)-based assessment was neither incorporated into the protocol nor conducted on these patients. In spite of lack of a structured adverse event assessment, carefully conducted short-term follow-up revealed no adverse device-related events at the skin graft donor sites. The treating physician was aware of the treatment group to which the patient was randomized, in view of the fact that the operational characteristics of the technology make investigator blinding challenging. However, blinding was taken into account for the primary outcomes assessment; a subject matter expert was used to provide blinded evaluation of timing and extent of donor site epithelialization for all study subjects. In addition, the control group was treated with one institutionally designated standard of practice, which is not uniformly adhered to in other burn and trauma centers. In fact, there are currently no accepted standards of practice with regard to wound care of STSG donor sites, so our control group represents but one of many methods used to provide donor site wound care. The existence of widespread variability in donor site wound care further illustrates the lack of data demonstrating a clearly superior wound care modality or approach in this population.

Despite the limitations of this study, the results are promising, namely, that of a novel approach with an existing technology having a minimal side-effect profile showing a significant effect on STSG donor site re-epithelialization. This marks the first time that ESWT has been demonstrated to have a significant effect on STSG donor site healing. Low-energy defocused shock wave therapy for donor site wounds addresses some of the unmet

needs for this clinical problem: comparable, if not greater, efficacy relative to current therapeutic approaches; noninvasiveness, highly favorable side-effect profile, no known drug interactions, time-efficient simplicity of use, and cost effectiveness. Although compelling, we believe that this study clearly identifies the need for further validation in a larger double-blinded study that is adequately powered to assess for multiple secondary outcomes measures of interest relating specifically to patients undergoing skin grafting, which include site-specific pain, patient quality of life, cosmetic results, and issues relating to long-term follow-up.

This study does demonstrate, however, that ESWT application to STSG donor sites is both safe and efficacious. A definitive phase III trial is planned to test the hypothesis that STSG donor sites treated with a single application of ESWT and standard of practice versus standard of practice alone will demonstrate a more rapid time to re-epithelialization. This planned study will also include long-term follow-up to allow for assessment of other secondary outcomes measures of interest to include patient quality of life, level of symptom distress, donor site pain, and degree of scarring.

In conclusion, this prospective randomized trial was undertaken to demonstrate the safety and efficacy of a novel wound healing technology in a defined population. A single application of ESWT followed by institution-specific standard of practice wound care was shown to significantly accelerate time to re-epithelialization compared with re-epithelialization time in patients treated with standard of practice alone among patients with STSG donor sites. Larger scale, double-blinded prospective validation of this technology using a generally acceptable standard of practice control, along with long-term follow-up and assessment of clinically relevant secondary outcomes measures is indicated. The ability to mollify donor site pain and improve quality of life during healing, as well as enhance the final cosmetic appearance would address an important, unmet need in surgery. Based on the findings of our previous phase II trial and the current phase III trial, we remain optimistic that unfocused, low-energy shock waves will represent a clinically relevant, practice-altering advance in wound care.

### Author Contributions

Study Conception and design: Ottoman, Hartmann, Thiele

Acquisition of data: Ottoman, Maier

Analysis and interpretation of data: Ottoman, Tyler, Schaden, Stojadinovic

Drafting of manuscript: Ottoman, Tyler, Maier, Schaden, Stojadinovic

Critical revision: Hartmann, Thiele, Schaden

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