Small Intestinal Submucosa Wound Matrix and Full-thickness Venous Ulcers: Preliminary Results

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Abstract: Recently developed wound care biomaterials derived from natural tissue sources have been shown to improve wound closure by stimulating granulation tissue deposition and epithelization of dermal wounds. These products may offer significant advantages to other available treatments for the management of venous ulcers. One such biomaterial, derived from porcine small intestinal submucosa (SIS), has shown promise as an effective treatment to manage full-thickness wounds. This is an interim analysis of a prospective, randomized, controlled, clinical trial currently being conducted to examine the effectiveness of SIS wound matrix in treating full-thickness venous leg ulcers. Patients meeting inclusion criteria were randomized to either receive treatment with the SIS wound matrix or a standard of care therapy. Ulcer size was determined at enrollment and weekly throughout treatment. Healing, as defined by full epithelization, was assessed at each visit for a period of up to 12 weeks. Complete wound closure within 12 weeks is the primary outcome measure. In this interim analysis, the authors include results from the first 84 evaluable patients enrolled in the trial. The authors found 71 percent of venous ulcers healing at 12 weeks with SIS compared to 46 percent with standard care, a significant group difference. The authors conclude that, in this subset of patients, the SIS wound matrix showed a higher incidence of wound closure as compared to standard of care treatment.

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Wound healing is a complex process of tissue restoration[1,2] that can either lead to fibrotic tissue replacement (scarring) with limited functional restoration or to the restoration of natural tissue with normal structure and function. An accepted goal of modern wound care includes facilitating the healing response toward the restoration of functional tissues. This goal is accomplished by providing a conducive environment for wound healing through the means of maintaining wound hydration,[3] offering thermal insulation, and providing protection from infection.

Current standard of care for venous ulcers provides these benefits, but many ulcers still fail to heal and become chronic wounds.[4–7] This poor success rate burdens society with monthly healthcare costs estimated at approximately $2400 for each venous leg ulcer.[8,9] The estimated annual treatment costs in the United States for hard to heal wounds is in excess of $1 billion.[11] It has also been noted that medical costs per episode are distributed evenly

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throughout treatment, suggesting that reducing the time to healing could result in a substantial decrease in the total amount of healthcare dollars required to care for wounds that fail to heal.[11] Thus, novel wound care alternatives that shorten the time to healing or result in increased overall healing rates are desired.

Wound care materials derived from biologic sources have been shown to effectively promote granulation and epithelization of dermal wounds.[12,13] In addition, biologic wound products have been shown to effectively regulate evaporation and exudation and to effectively protect the wound site from bacterial infection. One such biologic wound care product, a biomaterial derived from the pig small intestine submucosa (SIS) (Oasis®, Healthpoint Ltd., Ft. Worth, Texas), has been extensively evaluated in pre-clinical models and in clinical use since its unique properties were first reported in 1989.[14]

This novel material, a thin, translucent layer of the intestine, is approximately 0.15mm thick and consists primarily of a collagen-based extracellular matrix (ECM). However, unlike other purified collagen wound care products, other components of the ECM, such as glycosaminoglycans (i.e., hyaluronic acid),[15] proteoglycans, fibronectin,[16] and other matrix-associated factors, including basic fibroblast growth factor[17] and transforming growth factor-beta[18] are retained.

The first clinical report of the use of SIS to treat partial-thickness skin wounds was published in 2002.[19] A total of 14 patients with wounds were evaluated using the SIS wound matrix. Wounds re-epithelized within 10 weeks with minimal scar formation. It was further reported that in none of the 14 patients did the SIS wound matrix show signs of toxicity, clinical signs of rejection, or cause sub-epithelial seroma formation as the wounds progressed to full healing.

In this current investigation, the authors determined whether treatment of full-thickness venous leg ulcers with this collagen-based extracellular matrix SIS wound matrix would lead to a greater proportion of healed ulcers at 12 weeks versus standard care alone. Herein, the authors present interim data from this prospective, randomized clinical trial to assess the effectiveness of the SIS wound matrix in the treatment of full-thickness venous leg ulcers.

Table 1. Summary of patient inclusion criteria

Variable	Criteria
Patient age	≥18
Ulcer size	1-64cm^2
Ulcer depth	Extends through both the epidermis and dermis
Ulcer duration	>1 month
Ulcer location	Between and including the knee and ankle
Wound bed characteristics	Viable wound bed with granulation tissue

Methods

This prospective, randomized, controlled clinical trial is being conducted at multiple institutions across the United States and Canada. Currently, 84 patients have been enrolled, have completed the treatment protocol, and are considered evaluable for this interim analysis.

The study protocol and informed consent statements were reviewed and approved by either an independent institutional review board (IRB) or each study location's governing IRB. Prospective patients suffering from chronic venous insufficiency, as diagnosed by clinical presentation, and signing the informed consent were considered for inclusion if they met the additional criteria presented in Table 1. In addition to the inclusion criteria outlined in Table 1, all patients who met the criteria were required to undergo a two-week screening period prior to being enrolled. During the screening period, the target ulcer was treated with standard care and compression therapy. Ulcers that exhibited a greater than 50-percent reduction in surface area during the screening period were excluded from the trial. This screening period was designed to limit the study to only those patients having venous leg ulcers that would not quickly heal with compression therapy alone.

Patients were excluded from the trial for any of the following: arterial disease (ankle brachial index

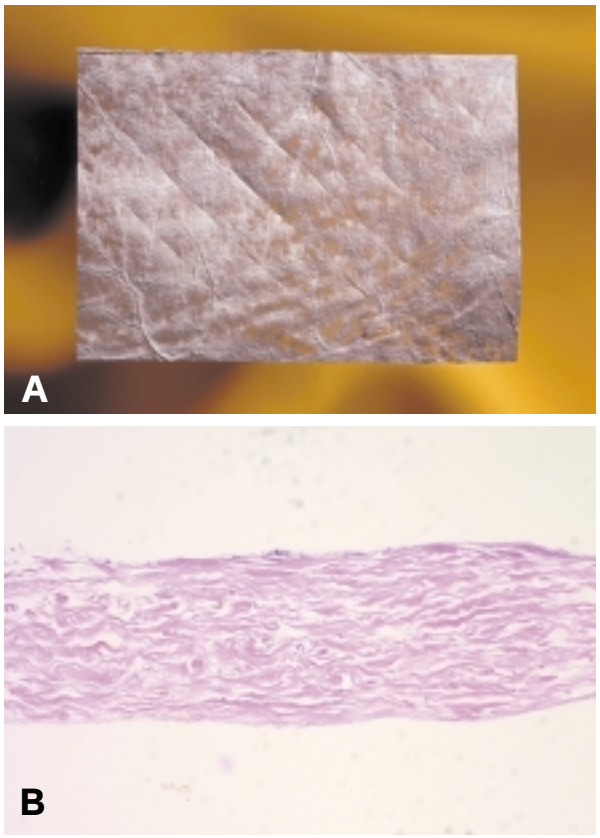

Figure 1. *Pictured here is the SIS Wound Matrix. The prepared SIS is an acellular collagen-based wound care product approximately 0.15 mm thick. A) Gross Image; B) H&E, Original Magnification, 100X.*

(ABI) less than 0.80); any known medical condition known to impair wound healing (vasculitis, rheumatoid arthritis, or other collagen vascular disease, malnutrition [albumin <2.5mg/dL], cellulitis, osteomyelitis, necrotic or avascular ulcer beds, uncontrolled congestive heart failure, uncontrolled diabetes [HgB A1c>12%], sickle cell disease); taking concomitant medication known to impair wound healing (corticosteroids, immune suppressives); a history of radiation therapy to the wound site; allergy to porcine products; clinical signs of infection; undergoing hemodialysis; or having religious or cultural objections to the use of porcine products.

Treatment of Ulcers

Patients were randomized to receive either the SIS wound matrix or a standard of care. The standard of care consisted of weekly wound cleansing, debridement (as necessary), dressing changes, and compression therapy. During the dressing change, wounds were cleansed with gentle irrigation and covered sequentially with a nonadherent dressing and a multilayer compression bandaging system.

All patients randomized to receive the SIS wound matrix (Figure 1) received the same dressing material, compression therapy, and type of care as patients randomized to the standard of care. The only difference between the groups was the added application of the SIS wound matrix directly onto the wound bed prior to the application of the other dressing materials. To apply the SIS wound matrix to the wound bed, ulcers were routinely cleaned, the sterile SIS wound matrix was cut to size slightly larger than the ulcer, placed upon the wound bed, and moistened with sterile saline. Secondary dressings were then applied after placement of the SIS to further protect the healing environment and to maintain direct contact of the SIS wound matrix with the wound bed. Repeat applications of the SIS wound matrix were applied weekly during a clinic visit.

Endpoints

The primary outcome measure was the incidence of complete wound healing by 12 weeks. Complete wound healing was defined as full epithelization of the wound with the absence of drainage. Patients whose wounds completely epithelized before 12 weeks stopped receiving treatment and were considered healed. Patients whose wounds failed to completely epithelize by 12 weeks were considered not healed and were given the choice of alternative treatments.

Secondary outcome measures will be examined following complete enrollment. These endpoints include the following: costs to healing; time to complete epithelization; rate of wound closure; adverse events; and ulcer recurrence during a six-month follow-up period. Ease of use and clinician satisfaction with the SIS wound matrix are also being recorded.

Statistics

The trial has been designed to allow detection of a 20-percent difference between treatment and control groups, with a five-percent alpha risk and an 80-percent study power. Following complete data analysis

the authors will be able to examine both the primary and secondary outcome measures. In this interim analysis, the authors report on only the primary outcome measure, the proportion of healed ulcers at 12 weeks in each group, and compare them using Fisher's Exact Test.

Results

Patients. Blind, prospective, randomization of study participants was used to eliminate bias in the assignment of treatment groups. To date, 84 patients have completed the 12-week treatment protocol out of the targeted enrollment of 180. Basic baseline patient characteristics for those included in this interim analysis are included in Table 2. Wound duration prior to onset of the study is also reported in Table 2 and found to be no different between groups. Study groups are also balanced with respect to patient age and gender.

Table 2. Baseline demographics for patients included in this analysis

	SIS (*n*=45)	Control (*n*=39)
Age, years, mean ± SD	62±17 Range: 21–90	65±16 Range: 41–91
Gender		
Male (%)	20 (44%)	17 (44%)
Female (%)	25 (56%)	22 (56%)
Ulcer Duration		
1–3 months	16 (36%)	11 (28%)
4–6 months	7 (16%)	6 (15%)
7–12 months	3 (7%)	3 (8%)
> 1 year	16 (36%)	15 (38%)
Unknown	3 (7%)	4 (10%)

Healing at 12 Weeks. Healing (complete epithelization with the absence of drainage) at 12 weeks was measured. At this stage of the trial, 71 percent (32/45) of patients receiving SIS wound matrix were considered healed versus 46 percent (18/39) of patients receiving standard of care alone (Table 3). The result demonstrates that the incidence of healing in the group treated with SIS wound matrix is significantly improved as compared to standard of care (p=0.018).

Table 3. Incidence of venous leg ulcer healing at 12 weeks

	Healed (%)	Not Healed (%)	Totals
SIS	32 (71%)	13 (29%)	45
Control Strategy	18 (46%)	21 (54%)	39
Totals	50	34	84

Discussion

Standard care treatments for venous leg ulcers include weekly wound cleansing, debridement (as necessary), dressing changes, and compression therapy. This standard of care has been reported to lead to healing after 12 weeks in only 34 to 40 percent of patients.[6,20] The standard of care used in this study led to healing in 46 percent. A reason for these poor results may well be the lack of any remaining matrix in the wound bed. Wound care products, such as SIS, that are derived from acellular ECM tissues and minimally processed to retain the three-dimensional architecture and composition of the ECM offer an ideal environment for healing wounds.[19] The complex composition of collagens, proteoglycans, glycosaminoglycans, and other ECM-associated factors found in the SIS wound matrix[15–23] should be able to provide the needed native tissue architecture for the propagation of new and healthy tissue, and a stable structure for cell attachment, proliferation, and differentiation.[19]

This clinical trial has been designed to study the effectiveness of SIS wound matrix for the management of full-thickness venous leg ulcers. Initial clinician feedback from this trial has revealed that the wound matrix is easy to apply, is nontoxic, and does not induce an adverse immunologic reaction, even in patients given repeated applications. The interim results demonstrate that placement of the SIS wound matrix on ulcers results in a significant improvement in 12-week healing rates compared to currently used standard of care treatments. These observations and initial clinical findings support preclinical findings in animal models[22] and support the initial observations of effectiveness in the human population.[19] Results indicate that the SIS wound matrix can be used to successfully manage venous leg ulcers due to its protective properties,

improving the wound healing environment and the ability to act as a natural template for tissue regrowth may also play a role.[23]

Conclusion

A biomaterial derived from the submucosal portion of porcine small intestine has been used successfully in pre-clinical studies of wound healing and in other surgical procedures where soft tissue reinforcement is indicated. This SIS biomaterial has now been developed into a wound care product that improves healing of full-thickness venous leg ulcers, compared to standard care, in a clinical population. This interim analysis was based on the number of evaluable patients instead of the complete intention-to-treat population, and thus the p-value associated with the completed clinical trial may be different. Nonetheless, these promising results justify further evaluation of this biologic matrix for its effectiveness in the treatment of these and other types of wounds.

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