ORIGINAL INVESTIGATION

Development of a Severity Scale for Evaluating the Need for Graftskin in Nonhealing Venous Ulcers

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ABSTRACT

OBJECTIVE: To construct an easy-to-use severity scale based on data from a multicenter venous leg ulcer trial to predict which wounds will progress toward closure and which will remain unhealed.

DESIGN: Factors that have an impact on wound healing (eg, ulcer duration, depth, area, location, and fibrin) were identified in the literature. A severity scale was constructed based on these factors.

SETTING: Multicenter clinical trial.

PATIENTS: 240 patients with venous leg ulcers of longer than 1 month's duration.

MAIN RESULTS: Wound duration and area were identified as having the greatest impact on ulcer healing. Using multivariate regression analyses, a wound score of 8 or less was considered mild to moderate. A severe wound, having a score of 9 or greater, was found to be unlikely to heal with compression therapy alone.

CONCLUSION: This severity scale can serve as an adjunctive tool in the prompt identification of ulcers with a poor healing prognosis and enable early intervention with alternate therapies. To optimize the severity scale, future trials should incorporate a method to review the interaction of known factors that impair wound healing.

ADV SKIN WOUND CARE 2002;15:66-71.

Venous leg ulcers are the most frequently occurring chronic wounds, accounting for 80% to 90% of all lower-extremity ulcerations.[1] An estimated 1% of the population is affected with venous leg ulcers, with an increased prevalence among the elderly.[2] Management of these chronic, commonly recurring ulcers is associated with considerable health care expenditures, particularly when managing hard-to-heal venous ulcers. The economic burden in the United States for 4 months of outpatient treatment has been projected to be between $775 million and $1 billion.[3]

The pathogenesis of venous leg ulceration involves chronic venous insufficiency secondary to valvular incompetence, which, in turn, leads to development of localized venous hypertension.[4] Various explanations attempt to illustrate the mechanism whereby venous insufficiency results in ulceration, including the sticky leukocyte hypothesis and the fibrin cuff theory.[5] The recently proposed sick-cell hypothesis suggests venous ulcer fibroblasts are rendered unresponsive to growth factors such as transforming growth factor-1 (TGF-1)—a cytokine integral to the synthesis of the extracellular matrix, consisting of collagen, proteoglycan, and fibronectin.[6]

The mainstay of therapy for venous ulcers remains compression therapy, which serves to control the underlying venous hypertension and improve venous return. A variety of methods are used to achieve these effects, including multilayer elastic compression bandages, inelastic paste boot systems (eg, Unna boot and Duke boot), graded compression stockings, or mechanical devices.[7,8] The time required for venous ulcers to heal with the use of conservative treatment regimens is variable. Studies have reported that 40% to 50% of venous ulcers will not achieve complete healing with standard compression therapy alone.[9-11] Eighty-one percent of patients with hard-to-heal venous ulcers of more than 1 year's duration do not heal with compression therapy within a 6-month period.[10] If complete wound healing is not attained by compression therapy alone, surgical intervention aimed at correcting the cause of venous insufficiency (eg, superficial vein stripping or subfascial endoscopic perforator surgery) or treatment by skin grafting may be required.[4]

FACTORS INFLUENCING HEALING

A variety of factors have been demonstrated to impact the rate and degree of venous ulcer healing; for example, ulcers of long duration are associated with a

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poor healing prognosis.[11] The initial venous ulcer area also affects wound healing, with large deep wounds requiring a longer time to heal than small deep wounds.[12] One study reported that a venous ulcer was 1.9 times more likely to heal if wound size was decreased by one half its initial area.[11] Initial wound depth also may affect the healing rate because a longer time is required for granulation tissue to form over a deep lesion and the adnexal structures that promote reepithelization are often absent in deep wounds.[1] Superficial venous ulcers are expected to heal faster than deeper ulcers extending to the subcutaneous tissues.

In addition, the degree of venous insufficiency was found to be a prognostic indicator of venous ulcer healing. Skene and colleagues determined the relative risk of healing for patients with superficial vein involvement (incompetence of long or short saphenous vein) to be 1.8 when compared with patients with deep-vein involvement (popliteal valve incompetence). This means that the wound was 1.8 times more likely to heal in the absence of deep-vein involvement.[11]

Furthermore, assessment of the wound bed can provide information regarding wound healing.[12,13] The presence of fibrin in the wound has historically been considered to be associated with a slower healing rate. True wound infection, in contrast to bacterial colonization of the wound, has also been found to be an impediment to proper healing.[14] Comorbidities known to contribute to impaired wound healing include arterial insufficiency, diabetes, cancer, sickle cell anemia, and immunologic disease.

Compression therapy may not always be sufficient to achieve complete and rapid wound closure of certain hard-to-heal venous ulcers. Studies have estimated that 50% of venous ulcers remain unhealed for more than 1 year.[2,15] Venous ulcers of long duration pose a particularly difficult management problem and negatively impact patients' health-related quality of life.[16] In addition, these wounds are associated with high costs attributable to increased hospital stays, office visits, and use of home health care resources.[3] To improve outcomes in these patients, strategies are required for early identification of hard-to-heal venous ulcers.

Table 1. SEVERITY SCALE FOR WOUND-HEALING PROGNOSIS

Parameter		
Severity Variable	**Assessment**	**Index Score*†**
Initial area	<500 mm^2	1
	>500 mm^2	2
Duration of ulceration	<6 months	1
	6-12 months	2
	12-24 months	3
	>24 months	4
IAET stages (depth) of ulceration	Stage II (superficial ulcer)	1
	Stage III (ulcer extending to subcutaneous tissue)	2
Presence of fibrin in wound bed	None	1
	Some	2
Location of ulcer	Above the ankle	1
	At or below the ankle	2

IAET = International Association of Enterostomal Therapists
* Index Score 5-8 = mild to moderate; venous ulcer should heal with standard compression therapy
† Index Score 9-12 = severe; venous ulcer most likely will not heal with standard compression therapy; may need to consider use of Graftskin

PROSPECTIVE TRIAL OF GRAFTSKIN

The advent of an allogeneic, bilayered, living skin substitute (Graftskin [Apligraf]); Organogenesis Inc, Canton, MA, and Novartis Pharmaceuticals Corporation, East Hanover, NJ) has expanded the available treatment options for chronic venous leg ulcers, particularly for those that do not respond to standard compression therapy alone. Graftskin consists of epidermal and dermal layers and is designed to be similar in structure and function to human skin. The underlying dermal layer is composed of living, human fibroblasts interspersed within a bovine-derived collagen matrix. The overlying epidermal layer consists of living human keratinocytes organized in a fully differentiated, stratified epidermis with an outer stratum corneum.

The efficacy of Graftskin for healing venous leg ulcers was demonstrated in a previously reported prospective, controlled, multicenter trial of 240 patients randomized to treatment with Graftskin plus compression (n = 130) or active control with multilayer inelastic compression alone (n = 110).[10] At trial week 24, more patients with venous ulcers of longer than 1 month's duration before the beginning of the trial achieved complete wound closure with Graftskin plus compression therapy when compared with treatment using compression therapy alone (57% vs 40% adjusted, P = .022; 55% vs 49% unadjusted, P = .365). A retrospective analysis with Cox proportional hazards regression was used to adjust for pooled data and factors known to impact wound healing, including baseline venous ulcer duration and wound area. In a subgroup post hoc analysis of 120 patients with hard-to-heal venous ulcers of more than 1 year's duration, 47% of ulcers were

Table 2. RESULTS OF MULTIVARIATE ANALYSES: EFFECTS OF COVARIATES ON FREQUENCY AND TIME TO COMPLETE WOUND CLOSURE

Covariate	Logistic Regression*		Cox Proportional Hazards Regression†	
	Odds Ratio	*P* Value	Risk Ratio	*P* Value
Duration of ulceration	0.46	.0001	0.52	.0001
Baseline area	0.69	.013	0.77	.024

*Used to assess the relationship between covariates and frequency of complete wound closure at 6 months.
†Used to assess the relationship between covariates and time to complete wound closure.

completely healed after 6 months of treatment with Graftskin plus compression therapy compared with 19% of ulcers treated with active control ($P < .005$, Fisher exact test). In addition, complete wound closure was achieved at a faster rate with Graftskin compared with active control ($P < .005$).[17] The original study was neither designed nor powered to assess long-term (>1 year) venous ulcer recurrence. This issue was outside the scope of the original study because ulcer recurrence is driven by underlying disease.

RATIONALE FOR SEVERITY SCALE

A simple method to quickly and noninvasively identify ulcers that will fail to heal with compression therapy alone would allow these wounds to be more quickly treated with effective therapy, reducing treatment costs and improving patients' quality of life. For this reason, the aim of this retrospective analysis was to construct a simple-to-use severity scale, based on initial venous ulcer characteristics, that could predict which wounds would progress toward closure and which would remain unhealed. The severity scale could be used as a tool in an office-based setting to help identify hard-to-heal venous ulcers unlikely to respond to standard compression therapy and those that may benefit from alternative treatment options, such as Graftskin. The severity scale would be used as an alternative to extensive vascular anatomy and functional status tests, such as angiography and Doppler duplex imaging, normally available in a vascular laboratory.

METHODS

Study design

This retrospective analysis was based on data from 240 patients with venous ulcers who participated in a prospective, multicenter, randomized, controlled, parallel group trial comparing the efficacy of Graftskin plus compression therapy with standard multilayer compression alone for the treatment of venous leg ulcers.[10]

Predictors of wound healing were identified prospectively based on examination of the venous ulcer literature. Primary factors included duration of the wound, location of the ulcer, size of the ulcer, stage or depth of the wound (International Association of Enterostomal Therapy [IAET] staging), and the presence of fibrin in the wound bed. Although wound infection was also found to influence healing, it was not considered in the present analysis because quantitative biopsy was not performed in the trial and true wound infection could not be determined. In addition, patients with comorbidities known to interfere with wound healing (eg, uncontrolled diabetes, cancer, immune deficiency, or arterial insufficiency) were excluded from the trial.[10]

A severity scale was constructed to predict the rate and degree of wound healing depending on the presence of 1 or more of these variables (Table 1). Each indicator was assigned a weighted score determined, in part, from data in the literature and results from multivariate regression analyses of the active control patients from the large, multicenter trial. The weighted scores for each ulcer were then tallied to obtain a cumulative score. This final value was the severity index and represented the likelihood of complete venous ulcer healing. The higher the score, the greater the severity and the longer the ulcer would likely take to heal. Possible scores on the severity scale ranged from 5 (mild) to 12 (most severe).

The severity scale was not available for use in the original trial because it was developed by post hoc analysis of data from the original trial. This study does not attempt to test the scale. The objective of this study was to retrospectively construct an easy-to-use severity scale to predict which venous ulcers would progress toward healing and which would not, based on the results of a large, multicenter, venous ulcer trial.

Study population

Patients ranging in age from 18 to 85 years were entered in the trial if they met the following inclusion criteria: venous insufficiency, defined by positive venous reflux test (venous refilling greater than 20 seconds) and clinical presentation (hyperpigmentation, varicosities, and lipodermatosclerosis); history of nonhealing venous ulcers of longer than 1 month's duration; and venous ulcers extending through the epidermis into dermal tissue (Stage II or Stage III) but not exposed to bone or tendon. Primary exclusion criteria included significant arterial insufficiency, defined by an ankle-brachial index (ABI) of less than 0.65; venous ulcer size of less than ½ x ½ inch (1 cm x 1 cm) or more than 4 x 8 inches (10 cm x 20 cm); or medical conditions, concomitant medications, or both, known to impair wound healing. A more detailed description of exclusion criteria are reported elsewhere.[10]

Table 3. FREQUENCY AND TIME TO COMPLETE WOUND CLOSURE CLASSIFIED BY SEVERITY INDEX

	Percentage of Patients with Complete Wound Closure at 6 Months (No. Closed/Total in Severity Subgroups)			Median Time to Complete Wound Closure (Days)		
Severity Index Score	Graftskin n = 130	Active Control n=110	*P* Value*	Graftskin n = 130	Active Control n=110	*P* Value†
5 to 8 (mild to moderate)	63% (41/65)	73% (45/62)	.26	90	87	.34
9 to 12 (severe)	48% (31/65)	19% (9/48)	.002	181	Not attained	.003

*Fisher exact test (2-tailed)
†Log-rank test

Treatment protocol and follow-up

In the multicenter trial, patients were randomized to receive either Graftskin plus compression therapy or active control treatment. Patients in the active control group were treated with standard multilayer compression therapy, consisting of a nonadherent primary dressing (Tegapore; 3M Health Care, St Paul, MN), gauze bolster, zinc oxide-impregnated paste bandage (Unna boot), and self-adherent elastic bandage (Coban; 3M Health Care, St Paul, MN). Patients randomized to the Graftskin treatment group had Graftskin applied directly to the ulcer site, followed by a 3-layer compression wrap consisting of a nonadherent primary dressing, a gauze bolster, and a self-adherent elastic bandage.

In the prospective study, up to 5 applications of Graftskin were allowed during the first 3 weeks of the study. If less than 50% of the venous ulcer was considered closed by clinical observation, another application of Graftskin was required; if more than 50% was closed, another application was not permitted.

From weeks 3 to 8, a fresh 3-layer compression wrap was applied weekly. If complete healing (full epithelization of the wound with absence of drainage) occurred by week 8, the patient was placed in elastic support stockings, providing graded support pressure, for the remainder of the study. If the venous ulcer had not healed by week 8, the compression wrap was continued until healing and then followed by compression stockings.

Patients in the active control group were given standard compression therapy alone for the first 8 weeks, followed by compression stockings for patients who had achieved complete healing during this period. Those who had not achieved healing by week 8 were continued on compression therapy until healing, followed by compression stockings.

Patients were assessed twice weekly in the first week, then weekly for the next 8 weeks. After 8 weeks, follow-up evaluations occurred every 3 months for 1 year. Primary end points for evaluating efficacy included the incidence of complete healing by 6 months after initiation of therapy and the time required for complete healing to occur.

Statistical analysis

Statistical analysis consisted of the Fisher exact test (2-tailed) to determine the frequency of venous ulcer healing at 6 months and the Kaplan-Meier life table analysis and log-rank test to determine time to complete closure. Covariates considered as having an impact on healing included venous ulcer duration, baseline ulcer area, ulcer depth, ulcer location, and presence of fibrin in the wound. Logistic regression analysis and Cox proportional hazards regression were used to evaluate the combined effects of these factors on the frequency of complete wound closure by 6 months and the median time to complete wound closure, respectively. Logistic regression weighted outcomes were based on covariates at a specific time point (ie, frequency of 100% wound closure at 6 months), with results reported as odds ratios (OR). Cox proportional hazards regression weighted outcomes were based on covariates over the entire study period (ie, frequency of 100% closure at any time during the study), with results reported as risk ratios (RR). An OR or RR greater than 1 denotes the specified variable has a positive impact on healing. Conversely, a score less than 1 denotes a negative impact of that variable on healing. Factors suspected to impact venous ulcer healing that did not demonstrate statistical significance were excluded from subsequent models. Results of the post hoc regression analyses served to validate the weighted scores assigned to each of the indicators on the severity scale.

RESULTS

Of the 240 evaluable patients, 130 were randomized into the Graftskin treatment group and 110 were randomized into the active control group. Baseline demographic characteristics did not differ significantly between the 2 groups.

Clinical assessments of the venous ulcers, based on the criteria of the severity scale, were performed and each ulcer

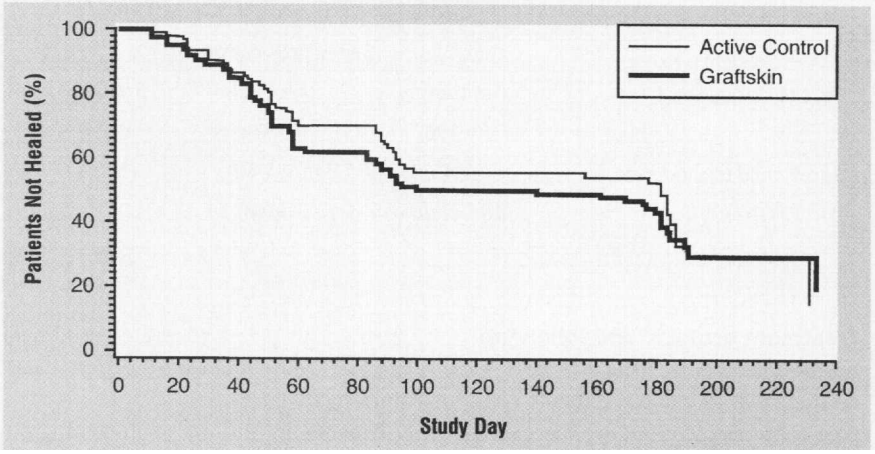
was assigned a severity index score. Subsequently, the venous ulcers were separated into 2 categories based on those scores. Ulcers with scores ranging from 5 to 8 were classified as mild to moderate; those ranging from 9 to 12 were classified as severe. A severe venous ulcer is unlikely to heal with compression therapy alone.

Duration was given the highest proportional weighting on the severity scale because it was considered to be the most significant variable affecting healing (OR = 0.46, P = .0001; RR = 0.52, P = .0001). Ulcer location, depth, and presence of fibrin were excluded from the final model because they did not demonstrate adequate statistical significance using a logistic regression analysis and Cox proportional hazards regression when data from the multicenter trial were reviewed retrospectively.

To validate the severity scale, post hoc multivariate regression analyses were performed to verify the weighted scores assigned to each factor on the scale. A Kaplan-Meyer life table analysis of all patients in the trial (Figure 1) shows little difference in healing between the treatment groups by 6 months. When these data are weighted by the factors considered to affect healing, however, the difference between treatment groups becomes apparent. A Cox proportional hazards regression for patients with all factors weighted shows patients healing more quickly with Graftskin and more patients healing by 6 months (Figure 2).

In the final model, independent factors determined to have the most significant impact on frequency and median time to 100% wound closure were venous ulcer duration and initial ulcer area (Table 2). For patients with prolonged ulcer duration (longer than 1 year), the odds of healing at 6 months were decreased by 54% compared with those having short ulcer duration (OR = 0.46; P = .0001). Patients with prolonged ulcer duration were 48% less likely to achieve complete wound closure at any time point compared with those with short wound duration (RR = 0.52; P = .0001). Similarly, the odds of achieving complete wound closure at 6 months were decreased by 31% for patients with venous ulcers having a large baseline area compared with those with small venous ulcers (OR = 0.69; P = .013). Furthermore, patients with large ulcers were 23% less likely to achieve complete wound closure at any measured time point compared with those with small ulcers (RR = 0.77; P = .024).

Figure 1. KAPLAN-MEIER LIFE TABLE ANALYSIS
This Kaplan-Meier life table analysis shows healing in patients treated with Graftskin plus compression therapy compared with active control.



The frequency of complete wound closure at 6 months and median time to 100% closure in patients with mild to moderate venous ulcers and severe venous ulcers are shown in Table 3. Results of this analysis indicated that Graftskin treatment was significantly more effective at healing severe venous ulcers when compared with the active control. Among severe venous ulcers, 48% of the Graftskin-treated patients achieved complete wound closure by 6 months compared with 19% of patients treated with active control (P = .002). In addition, severe venous ulcers treated with Graftskin healed significantly faster compared with severe venous ulcers treated with active control (P = .003). Among venous ulcers classified as mild to moderate, both treatment groups were equally effective in the frequency and time to complete wound closure.

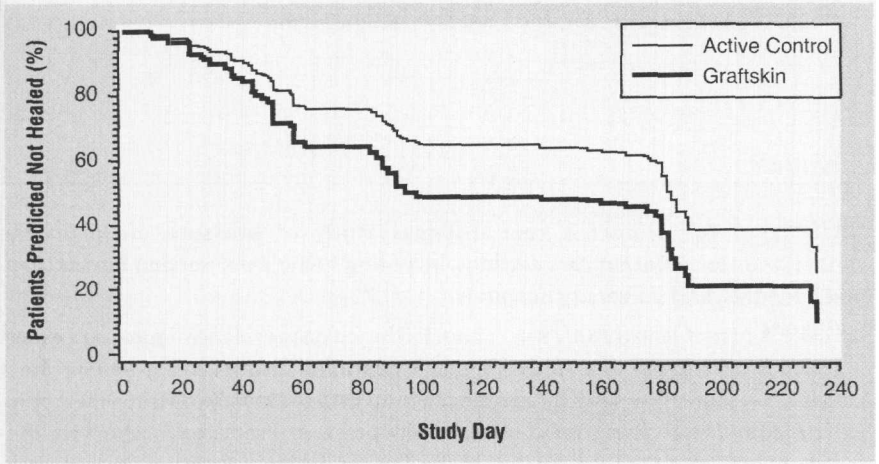
DISCUSSION

Major variables have been identified in venous ulcer literature as predictors of wound healing. These include wound duration, location, area, and depth and the presence of fibrin. A wound severity scale was constructed using these factors to serve as a predictor of complete wound healing. Post hoc regression analysis was performed to validate the severity scale, with wound duration and baseline area having the greatest impact on both frequency and time to healing.

The severity scale developed in this study was shown to be a valuable tool for identifying hard-to-heal venous ulcers that may not have adequately responded to conventional compression therapy. Treatment with Graftskin was found to be more effective than compression therapy alone in achieving rapid and complete closure of venous ulcers with a high severity index score (9 to 12); therefore, patients determined to have severe venous ulcers are most likely to benefit from treatment with Graftskin. This

Figure 2. COX PROPORTIONAL HAZARDS REGRESSION

This Cox proportional hazards regression had been adjusted for all factors, showing predicted healing in all patients with Graftskin plus compression therapy compared with active control.



finding confirms the results of earlier studies.[10,17]

A variety of algorithms and guidelines are available to aid clinicians in the decision-making process for diagnosis and treatment of venous leg ulcers.[18,19] Kistner and colleagues[19] have created an elegant, comprehensive classification and grading system for chronic venous disease, based on clinical manifestations, etiologic factors, anatomic distribution, and pathophysiologic findings (CEAP). The resultant CEAP classification system serves as the basis for a diagnostic algorithm used to determine the appropriate degree of evaluation for a clinical class of venous disease. However, this system may be most appropriate for vascular specialists and surgeons due to its complexity and requirement for objective testing using Doppler studies, duplex scanning, plethysmography, and phlebography. In addition, McGuckin and colleagues[18] developed a comprehensive, simplified diagnostic and treatment algorithm for use by specialists.

The long-term care of patients with chronic venous leg ulcers, especially those with hard-to-heal ulcers, is costly and requires use of considerable health care resources.[3] Higher treatment costs have been strongly correlated with wounds of longer duration; therefore, reduction in the time to venous ulcer healing is expected to result in decreased overall treatment costs. In addition, rapid and complete closure of venous ulcers has the potential to improve patients' health-related quality of life. This study demonstrated that prompt identification of venous leg ulcers associated with poor healing prognosis and early intervention with Graftskin may result in improved outcomes and may reduce the time and associated costs of treating these challenging wounds. The severity scale in this study uses readily available measurements and may be a generally applicable instrument for use by a broad range of health care professionals.

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