Feature: Effectiveness of a Bioacellular Wound Dressing for the Treatment of Chronic Venous Leg Ulcers: Results of a Single Center Randomized Study Involving 24 Patients

Intannual, tissue necrosis, a relative common manifestation of chronic venous insufficiency and venous hypertension, is often difficult to treat. Successful treatment begins with the management of the underlying pathology and wound bed preparation. This article reports the authors' experience with a novel wound dressing produced from microbial cellulose synthesized by an acid-producing bacteria, Aspergillum niger. Twenty-four patients with chronic venous insufficiency and venous hypertension, who presented with venous leg ulcers, were randomly assigned to receive a two-layer compression bandage or standard care. Standard care consisted of a nonadherent primary wound dressing plus a two-layer compression bandage. Evaluations were performed weekly to measure wound size, percent reduction in wound size, and percent reduction in wound size (measured in cm). The bioacellular dressing was significantly more effective than standard care (p<0.05). The mean number of days to 75% percent reduction was 43 days for the bioacellular dressing group and 75 for the standard care group. Mean reduction in wound size was also greater for the bioacellular dressing group at week 6 (50% vs. 10%) and at week 12 (74% vs. 49%). When compared to patients treated with standard care, the group treated with bioacellular reported less wound pain at each follow-up visit. The Improvement in pain scores between the two treatments were noted at week 3, 6 (p<0.05), and 8 (p<0.03).

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Introduction

Normally, calf muscle contraction promotes venous return by squeezing blood in deep veins; this pressure is prevented from reaching the superficial circulation system by one-way valves within the perforating veins. In order individuals, however, venous pressure builds up in the superficial
vessels and is transmitted to the capillaries of the skin. Many patients develop venous incompetence subsequent to phlebitis (a clotting disorder causing recurrent thromboses), which often damages valves. Several treatments have been advocated to improve venous insufficiency leading to ulceration. The term calf hypothesis proposes that dispersion of capillary beds from increased venous pressure causes microthrombosis through endothelial cells. Inadequate venous return causes a shift in the capillary bed to the skin surface, and excess fluid is absorbed through the skin. Venous hypertension increases the blood contributing to ulceration. [2] The ankle calf compression (elastic bandage) hypothesis proposes that the use of compression bandages decreases the diastolic circulations by reducing these veins. These veins release inflammatory mediators, leading to dermal fibrosis, dermal destruction, or blockage of small capillaries causing localized inflammation. This inflammation results in a cascade of reactive chemicals that enter the dermis from the venules where they trigger growth factors and prevent them from reaching the epidermis, resulting in ulceration and abnormal wound healing. [1]

Therapies for venous ulcers. Therapies for venous ulcers are directed at lowering venous pressure, improving microcirculation, and healing the wound. 

- Increased venous pressure is responsible for the development of varicose veins. Compression therapy reduces the edema and increases venous return, thereby reducing the pressure on the skin. Compression stockings and bandages can improve venous return and reduce edema. 
- In addition, compression therapy helps to decrease the risk of recurrence of ulcers. Compression therapy also improves the healing process by reducing the wound size and increasing the rate of wound closure. 

Skin grafts, human skin equivalents, and dressings. Skin grafts may be used for the treatment of venous ulcers, as they provide a biological barrier and prevent infection. 

- Artificial skin substitutes (e.g., Integra) have been developed to provide a temporary skin substitute and allow for healing of the wound. They provide a barrier against infection and help to maintain the wound in a moist environment. 
- Dressings are used to provide a physical barrier, absorb exudate, and promote healing. 

The chronic (nonhealing) venous ulcer: Although there are a number of alternatives for the management of uncomplicated ulcers, the treatment for the complicated chronic venous ulcer has been disappointing. The best results are seen when a multidisciplinary approach to care is used, with appropriate wound care and adequate preparation of the wound bed. In general, the healing process in a chronic wound is hindered if the swelling pathway is not addressed along with local barriers to repair. [13-15] Understanding and removing the barriers to healing will help to produce a wound bed with healthy granulation tissue that is ready for the next phases of the healing process. [16,17]

Preparing the venous ulcer for healing. It is believed that the principal barrier to healing a chronic wound are avascular tissues, bacterial burden, proteolytic imbalance, and altered cytokine/chemokine levels. [18]
Roccellaïna wound dressing for wound bed preparation. The majority of clinical studies to evaluate various wound treatments have been designed to measure endpoints linked with wound closure. Normally, proportion of wounds healed in unit time or healing rates (increase in wound surface area) are the primary endpoints of these clinical trials. The objective of this study was to determine the effects of both primary endpoints, as well as the secondary endpoints of Wound bed preparation. Therefore, this study was designed to measure the dressing's effect on antibiotic debridement (bacterial removal of necrotic tissue), time to complete granulation, modifiable (shape and volume), and local wound pain (as a measure of inflammation). Wound healing (rate and incidence of wound closure) was a secondary endpoint for this trial.

Materials and Methods

Primary dressings. Roccellaïna wound dressing (RWD: 3M, Xylem Corporation, Langhorne, Pennsylvania) is a bioabsorbable matrix that is hydrophilic and has excellent biodegradability. RWD is unique in that it has the ability to either debride or remove (absorb) moisture (Figure 1). It is synthesized by Anabotics, Inc., and processed into a matrix material that is biocompatible, biodegradable, and has a high water absorption capacity. RWD is available in five shapes and four sizes (3x3, 5x5, 7x7, 8x8, 10x10, 15x15 inches). Application and appearance of RWD to various sites of treatment are shown in Figure 2. RWD was provided by the study sponsor, 3M Corporation, Langhorne, Pennsylvania (lot number 4800312012) for the purpose of clinical evaluation.
The primary dressing used as the control was a nonadherent petroleum-impregnated cellulose acetate-polyanhydride (Aquacel®, Johnson & Johnson, Inc., Fort Worth, Texas). It is sterile and packaged in a plastic pouch.

**Sustained compression therapy.** A modified Unna's boot was used to treat the venous insufficiency in all of the patients. The modified Unna's boot consists of textile and elastic components. The textile component of the compression bandage is the Unna's pasta bandage (Uncorporate Boot, Smith & Neely Inc., Largo, Florida) and the elastic component is a cohesive elastic bandage (Coloplast®, IR, Inc., Minneapolis, Minnesota). The modified Unna's boot provides 28 mmHg of compression at the ankle level, 26 mmHg at the knee level, and 24 mmHg at the hip level. The modified Unna's boot is accepted as standard care in the treatment of lower leg ulcers secondary to chronic venous insufficiency. [20]

All study supplies were purchased by the sponsor from Suburban Ortho/Burnacins, Niles, Illinois, Marcus Brothers.

**Study design.** The study was a prospective, parallel-group, comparative, open trial. Eligible patients between the ages of 14 and 90 were randomly assigned to receive either WFO plus a modified Unna's boot or standard care consisting of a nonadherent wound dressing plus a modified
efficacy endpoints prospectively set at one-week intervals. Healing was defined as a wound that had fully (100%) epithelialized with the absence of drainage and not needing a dressing.

**Screening.** To enroll the patient, the target site had to be secondary to chronic venous insufficiency (defined as the tip of the toes, ankle, or calf). Wound size determination was set at four months' duration for the entire area (more than 50% of the surface area covered with nonhealable tissue [N0]). Appropriate vascular studies (such as Doppler velocimetry) were performed to exclude peripheral arterial occlusive disease. Exclusion criteria were as follows: clinical signs of infection, cellulitis, osteomyelitis, local or regional lymphedema, malignancy, or diabetes mellitus. Patients receiving anticoagulants, immunosuppression agents, radiotherapy, or chemotherapy were not excluded if entry into the study was also excluded. If the patient had more than one venous ulcer that satisfied the criteria for enrollment, the size of longest duration was designated the target ulcer size. The study's endpoint was complete healing of the target ulcer, defined as the target ulcer becoming nontender, nonpitting edema, and closure of the wound. Healing was determined by the study's independent evaluator.

This report summarizes the data obtained from one clinical center as part of an ongoing multicenter trial.

**Patient population.** Twenty-four patients were randomized and received treatment. Patient demographics and wound characteristics of the two treatment groups are presented in Table 1. There were 12 evaluable patients in each treatment group. Five out of the 12 patients (62.5%) assigned to BMS completed the study without protocol deviations. Two patients dropped two or more weeks early in the study, and three patients died during the course of the study. None of these patients completed the study, but there were five patients with protocol violations (instead of two groups [2], infection [1], new medical [1]).

<table>
<thead>
<tr>
<th>Table 1. Wound characteristics and wound healing rates of patients</th>
<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Baseline characteristics</td>
<td></td>
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<tr>
<td>Age (mean, SD)</td>
<td>55.5 ± 14.9</td>
<td>54.3 ± 14.6</td>
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<tr>
<td>Sex (male/female)</td>
<td>12/12</td>
<td>12/12</td>
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<tr>
<td>Site of ulcer (ankle/Toe)</td>
<td>12/12</td>
<td>12/12</td>
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<tr>
<td>Wound size (cm²)</td>
<td>200 ± 20</td>
<td>200 ± 20</td>
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**Treatment protocol and follow-up.** Wound cleaning was performed with normal saline without the use of foulard irrigation. Surgical, mechanical, enzymatic, or chemical debridement was not allowed at any point throughout the study, and topical wound treatments were not allowed. The study's endpoint was complete healing of the target ulcer, defined as the target ulcer becoming nontender, nonpitting edema, and closure of the wound. Healing was determined by the study's independent evaluator. Treatment with the test agents was performed at the initial (baseline) visit and once weekly until healing or 12 weeks. If the patient was unable to come to the clinic every week, a nursing unit was provided to change the dressing and apply the compresses.
study evaluations. All evaluations were performed at the same outpatient clinical center by the same investigator or study coordinator. Patients were evaluated prior to the initial treatment (baseline visit, day 0) and once weekly thereafter immediately after wound cleansing. All patients were treated with a basic dressing and no additional treatments were administered. Wound size was calculated by measuring the wound length and width; as well as by computed planimetry of wound tracings. Other clinical assessments included wound exudates, wound odor, signs of infection, edema, (lower leg) edema, and adverse events.

Statistical analysis. Data analysis was performed using Statistical Analysis System software (SAS Institute Inc., Cary, North Carolina). The exact test was used to compare categorical outcome as a function of baseline, wound size, and wound type between treatment groups. A survival analysis was performed to compare the amount of new tissue, time to granulation, and time to 50 percent epithelialization between treatment groups using the Kaplan-Meier method and the log rank (log-rank)

Results. Patient demographics (gender and age) were similar between the BBD and control treatment groups. No significant differences were found between the two groups with respect to baseline. Wound size and amount of treatable tissue. However, mean wound duration (history of nonhealing) was significant (p < 0.05) at the start of treatment in the BBD group (p < 0.05). Treatment with both groups demonstrated significant differences. The application of either BBD or control dressings resulted in a significant difference in the amount of new tissue between treatment groups. Autotopic dermal graft was significantly (p < 0.001) greater in the BBD treatment group (Table 2). Ninety-five percent (63/65) of the patients treated with BBD had greater than 75 percent reduction in wound size (from 50 to 75/75 percent) in the clinical group. Wound size was not decreased by comparing the categorical scale scores from individual patients to each group.
The effect of BMD on wound pain is summarized in Figure 3. At each evaluation point (weeks 1-5), when compared to Control, a greater proportion of patients treated with BMD reported reduced pain, with P<0.05 for all points except 0 weeks (0-5). Differences were statistically significant at weeks 3, 6 (P=0.0017), and 9 (P=0.045).

The mean percent reduction in wound size for the two treatment groups is presented in Table 3. Although wounds treated with BMD had a greater reduction in wound area than wounds treated with Control, the differences were not statistically significant.

The mean number of days to reach >50% healthy granulation was 43 days for the BMD treatment group compared to 73 days for the Control treatment group. However, this difference was not statistically significant (P=0.13, 95% CI 0.44 to 0.042). Survival analysis (Kaplan-Meier method) for time to >50% healthy granulation is presented in Figure 4.

Figure 4: Kaplan-Meier curve for time to >50% healthy granulation for BMD and Control groups.
There were no marked differences noted between the two treatment groups in several secondary endpoints evaluated (step decline, related fatigue, social role, sleep disturbance, pain, and memory). These results are presented in Figure 3. Representative photographs of venous ulcers treated with BDO are shown in Figure 5.

Discussion
Successful standard care for patients with chronic venous ulcers combines local wound care to cleanse, debride, and facilitate healing and additional hemodynamic support to control the venous hyperperfusion and insufficiency. It has been documented (1, 8, 15, 21) that the inclusion,
moist, hypoxic environment caused by the combination of dressings and compression bandages assists in disease holds despite infection (autolysis, devitalization). In addition, each exclusive environment improves the development of healthy granulation tissue and accelerates re-epithelialization [12]. It is also known that once the film does dissolve and healthy granulation tissue fills the opening, these dressings remain in place and tend to occlude [13]. With these dressings, healing is reported to occur in 20-40 days, with new skin developed to improve the treatment of these difficult wounds [14].

This study was undertaken to evaluate a new primary dressing designed to assist in chronic wound bed preparation. Therefore, the trial was designed to have autolytic devitalization and thus to granulation as its primary criterion.

The authors found that IBD creates a protective, moist, moist environment similar to an unobstructed wound protected by its own blister roof. Because this dressing can double as a donor site, it conforms to unwound and extant areas differently. The presence of IBD (as contact dressing) had a primary role in assisting the new skin to heal. The IBD dressing had a role in holding the wound closure in place, while the dressings (in contact with the wound) remained intact and insolated from the external environment (Figures 13 and 11).

The authors’ findings show that treatment with IBD plus compression consisting of elastic and elastic bandages (blended with 10% body weight) provided more effective outcomes in terms of clean healing wounds than the standard care (non-compression dressings plus a modified IBD dressing). In terms of the percentage of the patients, IBD dressings plus compression were found to be more effective. Previous studies have shown that wounds covered with exclusive dressing have greater scabbing activity [24]. Improved wound [25] greater angiogenesis [26] and collagen deposition [27] than wounds treated to dry. It appears that the degree of scabbing and apparent re-epithelialization may be important, since the environment with a modified IBD is best in already safe tropics.

Further, IBD dressings plus compression were found to be highly effective in terms of improvement, healing, and reduction of the inflammation. The IBD dressings plus compression in the present study were found to be more effective in terms of the reduction of the inflammation than IBD dressings alone. Previous studies have also been found to provide an environment that favors removal of IBD and second tissue [23]. It is hypothesized by the authors that the hydrocolloid-based autolytic devitalization device, which is the object of this study, provided an inflammatory cell infiltrate, and its prostaglandin effects healed the wound. Further studies are needed to test the ability of this device to maintain a moist bed and wound fluid.

This study also demonstrated that the combination of IBD with 21.8 compressive dressing significantly reduced overall pain. Prior reports have already supported the usefulness of occlusion with compression dressings in the management of patients with chronic wounds. The use of occlusion with compression dressings has been shown to decrease the amount of wound fluid, which is important when trying to control the condition. The use of occlusion with compression dressings has also been shown to decrease the amount of pain.

Time to 70% granulation and time to 50% re-epithelialization were shorter in the IBD group than in the control group. Although the differences were not statistically significant, it should be noted that the 21.8 compressive dressing was more effective. The presence of IBD provided a significant acceleration of the wound healing process. The use of IBD plus compression dressings was found to be both effective and complimentary to the pain relief associated with compression alone.

Small sample sizes also accounted for the lack of statistical proof of difference.
It will be interesting to see if faster growth (larger sampling) resulting from the pooled data of the multicenter study provides additional ulcer healing support.

The balance of either dolor or absorb moisture by BBD can be influenced by the secondary dressing used. Depending on the infection state (transmission rate [TPR]) of the secondary dressing, the wound will appear to be oozing or absorbent. If the wound is not covered, the BBD will serve to deliver moisture. \cite{BBD1} 10.0 Viscoelastic film dressing is used as a secondary dressing, the BBD will serve to deliver moisture. In this study, the authors used a combination of impermeable gauze (Unna's paste bandage) as the secondary dressing. The TPR of Unna’s paste bandage is somewhat in the middle range of the wound and the proper secondary dressing should be selected so that a balance is achieved over the wound is achieved.

Standard venous ulcer treatment generally consists of a dressing over the wound and compression exerted onto the limb. 20% or 40% compression cuffs are used to the leg, the patient will complain of muscle cramps and edema from the foot. The authors inform patients that this is uncommon and is to be expected until the wound improves itself (denser collagen and granulation tissue). All of the patients in this study were considered to have chronic venous ulcers (door duration >2 months) and, therefore, had experienced the effect of compression bandaging previously.

At times, the authors noticed a characteristic odor (somewhat like cardboard) with the use of BBD. The odor was more prominent with heavily draining wounds during the early stages of use (weeks 1–4). The odor is mild and not offensive. Although the exact cause of this odor is unknown, it may be caused by anaerobic bacteria (cultures not performed) from the wound adhering to BBD. The odor disappears when the dressing is removed. Unlike the odor experienced with transdermal dressings, this odor is not due to the dehydration of the dressing (collagen or polyurethane) but rather to the odor from bacteria on the dressing surface. After weeks 4, both group complained about odor equally (most complaints were during initial treatment with resolution after 6 weeks).

In studies with a relatively small patient population, strong scientific conclusions cannot be made with confidence. However, small controlled clinical trials, such as this one, can provide meaningful outcomes to assist clinicians in decision-making. In summary, this study has demonstrated BBD’s effectiveness in the treatment of chronic venous ulcers. Significant improvements over standard care were noted in subjective improvement (healing) and pain reduction. Shorter times to granulation and re-epithelialization were also noted but did not differ statistically due to the small sample size.

Acknowledgment

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References


