A Post-marketing Surveillance Study of Chronic Wounds Treated With a Native Collagen Calcium Alginate Dressing

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Abstract

Chronic wounds (ie, wounds that fail to progress through a normal, orderly, timely sequence of repair) continue to pose significant clinical and economic burdens. A prospective, descriptive, 3-week post-marketing surveillance study was conducted across 3 wound care centers in the United States to evaluate the effectiveness of a collagen calcium alginate dressing on chronic wounds in conjunction with standard care (SC) practices (eg, offloading, debridement, compression) to support healing. Eligible participants had to be >18 years of age, have at least 1 chronic wound, and no known sensitivity to collagen. Demographic characteristics were recorded at the screening visit on case report forms. At each visit, wound-related pain was assessed using the Visual Analog Scale along with wound characteristics including size (using digital planimetry), wound exudate (minimal, moderate, heavy), and odor (none, mild). Participants were monitored for adverse events as well as infection based on signs and symptoms in and around the local wound bed, the deeper structures, and the surrounding skin. An intention-to-treat approach was used for all analyses. If an observation was missing, the last observation carried forward principle was used. For wounds that healed, pain and exudate were set to 0 (no pain/exudate) at visit 4. Descriptive, paired *t* tests and the Wilcoxon signed rank test were used to analyze the data. Of the 31 participants (15 men, 16 women, mean age 66.6 years), most (13, 42%) had a diabetic foot ulcer or venous leg ulcer (10, 32%); median duration of all wounds was 148 days. Thirty (30) patients completed the study. The mean number of comorbidities was 10.6 ± 6.3, and patients used a mean of 9.3 ± 5.64 prescription or over-the-counter medications. For all wounds combined, mean wound area was 4.8 ± 8.38 cm^2 at baseline. At week 3, a decrease in wound area of 38.1% was noted (median: 45% ± 42.54; $P = .006$); 3 wounds healed completely. The change in wound exudate level from visit 1 to visit 4 was statistically significant ($P = .006$). No adverse events or infections occurred. In this population, the use of etiology-appropriate SC and a collagen calcium alginate dressing resulted in a decrease in wound area after 3 weeks of care. Longer-term studies to confirm these observations and controlled clinical studies to compare the effects of this dressing to other nongauze dressing treatments are needed.

Keywords: clinical study, wounds, diabetic foot ulcers, venous leg ulcers, dressings

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As the result of the aging population and an increase in the number of persons with risk factors such as diabetes, obesity, hypertension, and arterial insufficiency, the incidence of wounds is rapidly increasing.[1,2] Chronic ulcers in particular continue to pose a significant clinical and economic burden; in the United States alone, 6.5 million people are affected and an excess of $20 billion is spent on treatment annually.[1,2]

Venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) are among the most frequently encountered chronic ulcers in outpatient wound care practice.[2] Standard care (SC) in the treatment of DFUs includes debridement, offloading, and infection management; however, according to a meta-analysis[3] of 10 control groups from randomized controlled trials (RCTs), <30% of individuals with a DFU will heal within 20 weeks of commencing SC. A more recent randomized controlled trial by Zelen et al[4] revealed mean time to healing for DFUs treated with SC alone was 57.4 days compared to 23.5 days for dehydrated human amnion/chorion membrane

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(EpiFix; MiMedx, Marietta, GA) and SC and 47.9 days for a bilayer bioengineered skin substitute (Apligraf; Organogenesis, Canton, MA) and SC. Patients with unresolved ulcers are at risk of cellulitis, osteomyelitis, and amputation. According to evidence-based guidelines presented at a National Institute of Health conference by a panel of advisers,[5] if a DFU does not decrease in area by 40% after 4 weeks of care, advanced wound therapies should be used.[5]

VLUs treated using multilayer compression therapy also can take months to heal completely. With multilayer compression therapy alone, healing rates range from 30% to 60% at 24 weeks and 70% to 85% by year 1, according to a retrospective cohort study by Margolis et al.[6] A 12-month recurrence rate is estimated to be between 18% and 28%.[7] Thus, management and prevention of recurrence should be a priority. Adjunctive therapies with advanced wound care modalities are recommended with SC if progress in healing is not made within 30 days.[6]

In nonhealing wounds, the extracellular matrix (ECM) is disrupted or destroyed and cannot support wound healing. Therefore, it is believed that treatment strategies designed to replace the absent or dysfunctional ECM may be beneficial.[8] Natural collagen dressings are thought to facilitate healing in the preparation of the wound bed. Collagen has been shown to have an essential role in reducing inflammation, providing a matrix for remodeling and acting as a sacrificial substrate for proteases.[8] Cutimed Epiona (BSN medical, Hamburg, Germany), a collagen dressing that contains 90% native collagen and 10% calcium alginate, offers a native 3-dimensional (3D) matrix structure that is hypothesized to support the capture and binding of excessive proteases and inflammation-inducing factors in addition to providing support for the proliferation of cells needed for wound repair.[9] The dressing's flexible, open-porous 3D structure is designed to allow the collagen to function like an ECM scaffold in which fibroblasts can attach to the dressing and proliferate more rapidly to support granulation tissue ingrowth.[9] A working group of experts found the dressing has the potential to accelerate healing in wounds that have not responded to basic wound care.[8]

The objective of this prospective, descriptive surveillance study was to evaluate the effectiveness of a collagen dressing administered in conjunction with SC (ie, etiology-appropriate provision of debridement, cleaning, cover dressing, and offloading) in the treatment of chronic wounds over 3 weeks (4 visits: weeks 1, 2, 3, and 4).

Methods

Setting and participants. A prospective post-marketing surveillance study was conducted at 3 wound care centers in the United States. All patients 18 years of age with at least 1 chronic wound (defined as a wound that fails to progress through a normal, orderly, timely sequence of repair[10,11]) or any wound in which healing was delayed, stalled, hard to achieve, complex (ie, having 1 or more complicating factors such as exudate, infection, and comorbidities), or not responding to previous treatment, and with no known sensitivity to bovine collagen or other contents of the collagen dressing were included in the study. Participants with third-degree burns and persons who had received an experimental drug or medical device within 7 days before the start of the treatment visit were excluded. In patients with more than 1 wound, the largest wound was included in the study (if other ulcerations were present, they had to be at least 2 cm apart).

Institutional Review Board approval was obtained from the Western Institutional Review Board (Pr. No.: 20151675) and all patients provided written informed consent before study enrollment.

Ostomy Wound Management 2018;64(4):38–43

Key Points

- The authors evaluated wound outcomes of etiology-appropriate standard care and a collagen calcium alginate dressing for a period of 3 weeks in 31 patients with chronic wounds and multiple comorbidities.
- No adverse events occurred and the average wound size was significantly smaller after 3 weeks (average reduction 38%).
- Longer-term studies are needed to evaluate healing outcomes of this treatment approach and to compare it to other nongauze dressing regimens.

Table 1. Secondary dressings (N=31)

Wound type	N (%)
Diabetic foot ulcer	
ABD pads[a]	10 (76.92)
Xtrasorb[b]	1 (7.69)
Gauze	2 (15.38)
Venous leg ulcer	
Drawtex[c]	1 (10)
ABD pads	9 (90)
Traumatic wound	
ABD pads	3 (75)
3M 2 layer lite[d]	1 (25)
Pressure ulcer	
ABD pads	2 (100)
Surgical wound	
ABD pad	2 (100)
Mixed etiology wound	
Gauze	1 (100)

[a]Dukal Corporation, Ronkonkoma, NY; [b]Derma Sciences, Plainsboro, NJ; [c]Drawtex Healthcare, Fort Worth, TX; [d]3M, St Paul, MN

Table 2. Patient demographics (N=31)

Patient variable	Count N (%)	Mean/Median (SD)
Gender		
Male	15 (48)	
Female	16 (52)	
Age (years)	—	66.6/64.0 (14.20)
Race		
Caucasian	28 (90)	—
African American	3 (10)	—
Smoking		
Yes	3 (10)	—
No	28 (90)	—
Body mass index	0 (0)	
Underweight	7 (23)	—
Normal weight	5 (16)	—
Overweight	14 (45)	—
Obese	5 (16)	—
Morbidly obese	—	—
Patient comorbidity count		10.6/9.0 (6.33)
Most common patient comorbidities		
Diabetes mellitus	20 (65)	—
Neuropathy	15 (48)	—
Hypertension	21 (68)	—
Chronic heart failure	4 (13)	—
Coronary heart disease (CAD)	8 (26)	—
Dyslipidemia	11 (36)	—
Arthritis/osteoarthritis	7 (23)	—
Peripheral vascular disease	4 (13)	—
Renal insufficient/failure	2 (7)	—
Cancer	4 (13)	—

Table 3. Use of prescription and over-the-counter medications (N=31)

Patient variable	N (%)	Mean/ Median (SD)
Drug count	—	9.3/9 (5.64)
Selected drug categories (by indication)		
Pain	19 (61)	—
Neuropathic pain	13 (42)	—
Wound pain	1 (3)	—
Diabetes mellitus management	15 (48)	—
Dyslipidemia/high cholesterol treatment	15 (48)	—
Mental health illness treatment	7 (23)	—
Renal disorders management	2 (7)	—
Hypertension treatment	23 (74)	—

Treatment. SC was provided according to wound etiology. DFUs were offloaded, and VLUs received compression; all study wounds were surgically debrided as clinically indicated and cleansed with saline solution. The dressing was applied weekly and used in accordance with the application recommendations specified by the manufacturer and clinical requirements. The choice of secondary dressings depended on the type of wound, exudate, and patient characteristics; secondary dressings were used at the principal investigator's discretion (see Table 1). At each visit, wound-related pain was assessed using the Visual Analog Scale. Wound assessments were captured on all visits using digital planimetry (ARANZ Medical, Christchurch, New Zealand). Wound characteristics (exudate [minimal, moderate, heavy] and odor [none, mild]) were noted. Participants were monitored for infection and adverse events throughout the study. Presence of infection was evaluated based on clinical signs and symptoms around the local wound bed, the deeper structures, and the surrounding skin. A participant was considered to have completed the study if he/she had completed all visits or his/her wound healed and the confirmation of healing visit occurred as part of the study.

Data collection and analysis. Data were documented on case report forms and grouped for analysis. For medication grouping, selected indications were reviewed including pain, neuropathic pain, wound pain, for diabetes, dyslipidemia/high cholesterol, renal disorders, hypertension, and mental illness. Wound area was grouped by type of wound, but pain and exudate were not categorized by wound type. Body mass index (BMI; height x weight) was calculated and grouped by underweight, normal weight, overweight, obese, and morbidly obese.

An intention-to-treat (ITT) approach was used for all analyses. For missing observations, the last observation carried forward principle was used. For wounds that healed, wound area, pain, and exudate level were set to 0 at visit 4. Study variables were summarized as means and standard deviations (SDs) for continuous variables unless the data were non-normal, as determined by the Shapiro-Wilk test, in which case medians also were reported. Proportions or percentages were used to outline categorical variables. Paired *t* tests were used to compare endpoints if data were normally distributed, and the Wilcoxon signed rank test was applied if the data were non-normal and differences existed. To adjust for the family-wise error rate, *P* values were reported using the Hochberg step-up procedure. Adjusted 2-sided *P* values $<.05$ were considered significant. Data were entered into PASW 19 (IBM, Armonk, NY) to perform the statistical testing.

Table 4. Selected wound characteristics (N=31)		
Wound variable	**N (%)**	**Mean/ Median (SD)**
Type		
Diabetic foot ulcer (DFU)	13 (42)	—
Venous leg ulcer (VLU)	10 (32)	—
Traumatic wound	4 (13)	—
Pressure ulcer (PU)	2 (7)	—
Mixed etiology ulcer	1 (3)	—
Surgical wound	1 (3)	—
Initial area (cm²)		
All	—	4.8/1.8 (8.38)
DFU[a]	—	2.1/1.5 (1.68)
VLU[b]	—	8.9/2.3 (13.21)
Traumatic	—	1.6/1.5 (1.13)
PU[c]	—	0.5
Mixed etiology	—	15.8
Surgical	—	11.2
Wound history at first visit (days)	—	301/148 (370.17)
Location		
Forefoot	1 (3)	—
Mid and hindfoot	10 (32)	—
Heel	3 (10)	—
Ankle	5 (16)	—
Leg	10 (32)	—
Other	2 (7)	—
Exudate level at first visit		
Minimal	18 (58)	—
Moderate	11 (35)	—
Heavy	2 (7)	—
Odor level		
None	28 (90)	—
Mild	3 (10)	—

Table 5. Wound exudate levels at first and last visit (N=31)				
Week	**None N (%)**	**Minimal N (%)**	**Moderate N (%)**	**Heavy N (%)**
1	0 (0)	18 (58)	11 (35)	2 (7)
3	5 (16)	18 (58)	8 (26)	0 (0)

Shift from week 1 to week 3 was statistically significant (P=.006)

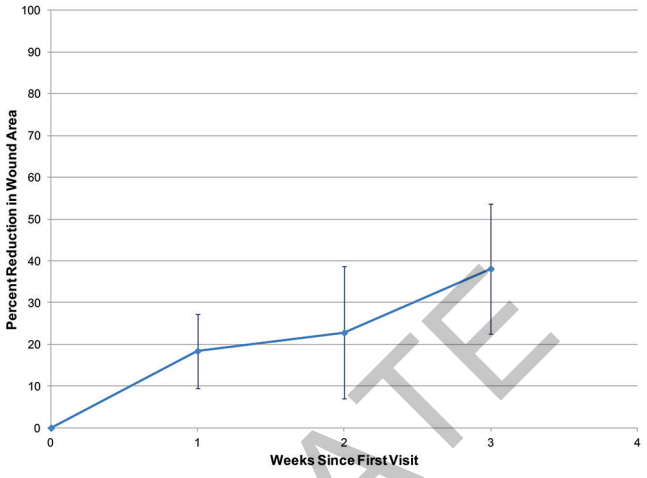

Figure. Mean percent reduction in wound area (N=31). The change in area between week 1 and week 4 was statistically significant (*P*=.006). Vertical bars: 95% confidence intervals.

Results

Of the 31 patients screened (15 men, 16 women, mean age 66.6 years), 30 completed the study (97%); 1 patient dropped out after 2 weeks. Four (4) missed the week 2 visit and 1 missed the week 3 visit. Most (90%) of the patients were Caucasian; 10% were African American. The study population was composed of individuals with many serious comorbidities; the mean number of comorbidities per patient was 10.6 (see Table 2). Nearly two thirds of the patients were overweight or obese (61%) and a high proportion had diabetes (65%), hypertension (68%), or neuropathy (48%). Patients used a mean of 9.3 prescribed or over-the-counter medications; the majority were for hypertension (74%), pain (61%), and diabetes management (48%) (see Table 3).

Four (4) patients had multiple wounds; 27 had 1 wound. Seven (7) patients had experienced prior amputations, 6 of whom had DFUs and 1 had a Stage 2 pressure ulcer on the heel as well as a history of peripheral vascular disease and neuropathy. The majority of ulcers in the study were DFUs (42%) and VLUs (32%) (see Table 4).

Mean wound area at first visit was 4.8 ± 8.38 cm² but varied considerably by etiology; for example, the mean area for DFUs was 2.1 ± 1.68 cm² and for VLUs was 8.9 ± 13.21 cm² (see Table 4). The mean duration of the wound at first visit was 301 days; wound age was not grouped by wound type.

Of the 13 DFUs, 12 were offloaded, 6 using total contact casting (TCC; 46%); other offloading methods included Charcot restraint orthotic walker (2 [15%]), offloading shoe (3 [23%]), and a wheelchair (1 [8%]), and 1 (8%) was not offloaded. All VLUs (7 [70%]) received compression using 3M 2-layer compression bandages (3M, St Paul, MN), while

others were provided Unna boot (1 [10%]), Tubigrip (1 [10%] minimal compression; Mölnlycke Health Care, Norcross, GA), and unspecified multilayer compression wraps (1 [10%]). Surgical debridement was provided as clinically indicated as follows: no debridement (4 [13%]), 1 debridement (13 [2%]), 2 debridements (5 [16%]) 3 debridement (6 [19%]), and 4 debridements (3 [10%]).

Of the 30 patients who completed the study, 13 reported wound-related pain at their first visit. Mean pain score at visit 1 was 1.6 ± 2.36, and mean pain reported at visit 4 was 1.3 ± 2.05. These differences were not tested statistically. On the other hand, 3 reported some level of pain at visit 4 when they had reported no pain in visit 1.

The proportion of patients with heavy/moderate amounts of exudate decreased between visit 1 and 4 (P = .006; see Table 5). The mean wound area for all wounds at the first visit was 4.8 ± 8.38 cm^2. The reduction in wound area 3 weeks after the first visit was 38.1% (median: 45% ± 42.54) (P = .006) with steady reductions week by week (see Figure). Of the 31 wounds, 14 (45%) were reduced by 50% or more after 3 weeks (7 DFUs, 3 VLUs, 2 traumatic wounds, 1 surgical wound that was 26 days old at first visit, and 1 pressure ulcer). Complete wound healing occurred in 3 wounds (10%) (2 VLUs and 1 traumatic wound). No infections or adverse events occurred during the study (see Table 4).

Discussion

Although a small number of chronic wounds will respond to SC, complete healing can take months.[3,6] Most of these wounds resist healing due to several factors, such as the severity of the ulcer and the patient's health status.[12]

A number of patients in this study were overweight or obese; had diabetes, hypertension, or neuropathy; and were taking prescribed or over-the-counter drugs for hypertension, pain, and diabetes. Despite these serious comorbidities, their wounds started healing after patients were enrolled in the study.

Although studies exists regarding the effects of using different collagen dressings (eg, collagen with alginate, collagen with hyaluronic acid, collagen with silver), the current authors found results of previous research vary/conflict for each type of dressing. The authors suggest this would be a good topic for systematic review.

Limitations

Although this study provides evidence that native collagen dressing may be more effective than SC alone, further controlled clinical studies to expand on these promising results should include the use of consistent secondary dressings, offloading, and compression devices. Follow-up studies should examine biofilm activity and explore how collagen dressing influences the microbial population in chronic wounds. Comparative effectiveness research is also needed; future studies should investigate the effect of different collagen dressings. With the continued focus on cost of wound care management, it is pertinent to evaluate the cost-effectiveness.

Conclusion

In this prospective, descriptive, post-marketing surveillance study, 31 patients with a variety of chronic wounds received appropriate standard wound care and a marketed collagen/alginate dressing for a period of 3 weeks. During that time, 3 wounds healed completely, no adverse events occurred, wounds reduced in size an average of 31.8%, and the proportion of wounds with heavy or moderate exudate decreased over the study duration. These results suggest that adding this dressing to SC practices, including offloading DFUs and providing compression for VLUs, has the potential to improve outcomes in patients with chronic wounds and comorbidities that may affect their healing potential. Future controlled clinical studies to ascertain the efficacy of this dressing compared to other nongauze dressing regimens are warranted. ■

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