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Leg Ulcer Treatment Outcomes with New Ovine Collagen Extracellular Matrix Dressing: A Retrospective Case Series

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ABSTRACT

The purpose of this study was to describe the rate of closure observed in venous leg ulcers during treatment with ovine collagen extracellular matrix dressings and compression. Fourteen patients with 23 wounds were retrospectively evaluated with respect to healing rates, time to closure, and weekly facility charge fees.

KEYWORDS: ovine collagen extracellular matrix, wound care dressing, venous leg ulcer

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INTRODUCTION

Venous leg ulcers (VLUs) account for up to 80% of lower-extremity ulcers in the United States[1] and are commonly associated with pain, itching, altered appearance, loss of sleep, substantial disability, social isolation, depression, and disappointment in treatment.[2–4] Treatment costs for VLUs, which are directly associated with time to achieve complete closure, can average more $4000 per month and between $16,000 and $40,000 per treatment episode.[4–6] Despite renewed focus on prevention and treatment, an estimated 3 million Americans are currently living with a VLU,[7] amounting to an estimated $1.9 to $2.5 billion in annual healthcare costs.[8] These costs do not include the financial toll imposed by VLU-related limitations on mobility and work capacity, patient out-of-pocket expenses, and psychological effects.

In addition to underlying venous insufficiency, elevated matrix metalloproteinase (MMP) levels play a major role in the pathophysiology of VLUs, contributing to disruption or damage of the extracellular matrix (ECM).[9,10] Compression therapy is considered a standard management strategy for venous ulcers; its positive effect on venous ulcers is clearly supported by a large body of evidence.[11] Yet, compression therapy in itself is often insufficient to heal the wound within an acceptable timeframe.[4] For example, with compression only, complete VLU closure rates of 50% to 65% at 6 months have been reported.[12–14] Approximately 20% remain unhealed at 2 years, and approximately 8% remain unhealed at 5 years.[15]

Although general superiority of 1 dressing over another in treating venous ulcers has not been demonstrated in the literature,[16] recent studies have identified the role of collagen-based ECM dressings in improving wound healing by reducing inflammatory mediators.[17–19] Use of decellularized ECM-based products in a variety of applications has increased during recent years because of the relatively rapid vascularization of these biomaterials, generally leading to improved healing outcomes.[20–22] Collagen matrices restore balance at the microenvironment level through binding and inactivation of excess MMPs while providing moist wound healing and protecting the biologic activity of endogenous growth factors.[23,24] Intact collagen ECM (CECM) dressings allow structural support for tissue regeneration, as well as provide cytokines and growth factors in physiologic concentrations.[25]

An established regimen of treatment using compression and collagen dressings has been shown to be effective in improving outcomes and healing in venous ulcers.[23,26] However, most collagen dressings are effective for up to 72 hours and require dressing plus compression changes every 3 to 4 days.[18,23]

A new ovine-based CECM dressing (Endoform dermal template; Mesynthes Ltd, Wellington, New Zealand; distributed by Hollister Incorporated, Libertyville, Illinois) has recently been cleared by the Food and Drug Administration for use in dermal applications, including treatment of chronic and acute wounds. The dressing is prepared from propria submucosa of ovine forestomach tissue using processes to delaminate and decellularize the tissue.[27,28] The CECM dressing contains 90% natural, intact collagen and 10% secondary ECM components. This collagen dressing is effective up to 7 days, which may translate into cost savings, versus traditional collagen dressings that typically require twice-weekly dressing changes.

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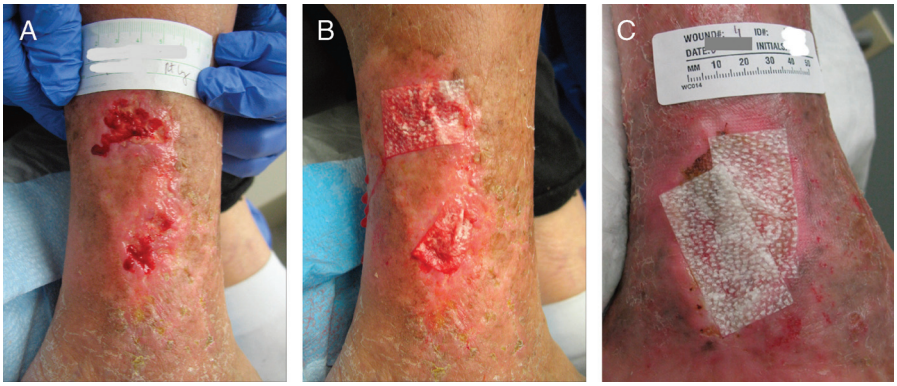
Figure 1A–C.
CECM DRESSING APPLICATION



A, Wound bed is prepared, including sharp debridement and irrigation, prior to CECM dressing application. B, Collagen ECM dressing may be cut to fit the wound dimensions or may overlap the wound edges. C, Collagen ECM dressing is hydrated with sterile saline prior to application of cover and compression.

The purpose of this study was to describe wound closure outcomes in VLUs during treatment with CECM dressing. Clinic records of patients with VLUs treated with CECM dressings were retrospectively reviewed to determine rate of wound healing, days to wound healing, and number of weeks in care.

METHODS

A retrospective review was conducted of medical records of consecutive patients who were treated with CECM dressing. Approval for this study was granted by the clinic's institutional review board. Outpatients 18 years or older with at least 1 venous ulcer treated with CECM dressings in the clinic between February 1, 2012, and December 31, 2012, were included in the analysis.

The CECM dressing was applied according to instructions for use by a team of clinicians (Figure 1A–C). Excisional debridement was performed at the initial dressing placement, and selective sharp debridement was subsequently performed as needed (Table 1). Using aseptic technique, a dry sheet of CECM dressing just larger than the ulcer was trimmed to overlap wound margins and placed on the wound bed. The CECM dressing was hydrated with sterile saline as outlined in the instructions for use. Light pressure was applied to the dressing to ensure it conformed to the underlying wound bed.

A sheet of petroleum jelly gauze was applied over the CECM, followed by 10 × 10-cm secondary gauze dressing, rolled gauze if needed, then the compression system. The number of patient wounds that received each of various compression systems is listed in Table 1. Each patient was followed up twice weekly: 1 nursing clinic visit on day 3 and 1 physician clinic visit on day 7. At the nursing visit on day 3, the compression wrap and dressing cover were changed, and the CECM dressing remained in place. At the physician clinic visit on day 7, debridement was performed if needed, and CECM dressing and compression were reapplied. Application of CECM dressings was discontinued when the wound was re-epithelialized.

Charts were reviewed for patient demographics, wound dimensions, total treatment time, number of weeks to heal, and current procedural terminology charges. Data were deidentified and imported into a Microsoft Excel spreadsheet. Data analysis was performed with SAS Software version 9.0 (Cary, North Carolina).

Table 1.
TYPES OF DEBRIDEMENT AND COMPRESSION USED DURING THE STUDY PERIOD

Wound Therapies	n (Patient Wounds)	%
Debridement		
Excisional debridement	23	100
Selective sharp debridement	9	39.1
Compression		
3-layer compression wrap	12	52.2
4-layer compression wrap	14	60.9
Self-adherent 2-layer wrap	10	43.5
Self-adherent, light 2-layer wrap	1	4.3
Single-layer, long-stretch wrap	1	4.3
Elasticated tubular bandage	1	4.3
Zinc oxide/calamine–impregnated gauze	2	8.6

RESULTS

Data from 14 patients with 23 VLUs treated with CECM dressings were analyzed. Ten of the patients were men (71.4%); the average patient age was 55.3 years (range, 37–78 years). Demographic and outcomes data are detailed in Table 2. The average surface area at CECM dressing initiation was 3.7 cm^2 (range, 0.2–23.4 cm^2). A total of 23 of 23 wounds (100.0%) healed during the study timeframe with CECM dressings during an average of 7.3 weeks (range, 2–15 weeks). One wound (10A) was treated with CECM dressings for 4 weeks until the surface area was 0.06 cm^2, at which time the investigator determined that CECM dressings could be discontinued. Wound 10A healed spontaneously, whereas wound 10B on the same patient continued to receive CECM dressing applications.

Of the 23 wounds that healed, 22 (95.7%) were healed within 12 weeks. Wound 10B was healed at 15 weeks. Total number of wounds open/closed per week is charted in Figure 2. Wound 12C was completely closed at week 11, but the ulcer reopened the following week, then was closed again on week 14. All other ulcers remained closed during short-term follow-up.

Average surface area reduction of all wounds was 97.9% at 12 weeks. Wounds healed at an average rate of 0.88 cm^2 (range, -0.1 to 11.7 cm^2) per week. A life table method survival analysis (SAS proc lifetest method = lt) indicated that 50% of wounds treated with CECM were closed by 7 to 8 weeks. There were no adverse effects or events associated with CECM reported in any of the patients during the study.

According to the hospital chargemaster committee, an average facility fee of $233.50 was charged at the midweek (day 3 or 4) visit for nursing compression wrap and dressing cover change. Dressing supply and application costs were bundled within this charge. This midweek visit was a nurse visit, not a physician visit, and therefore, no professional fee was charged.

PATIENT CASE STUDY

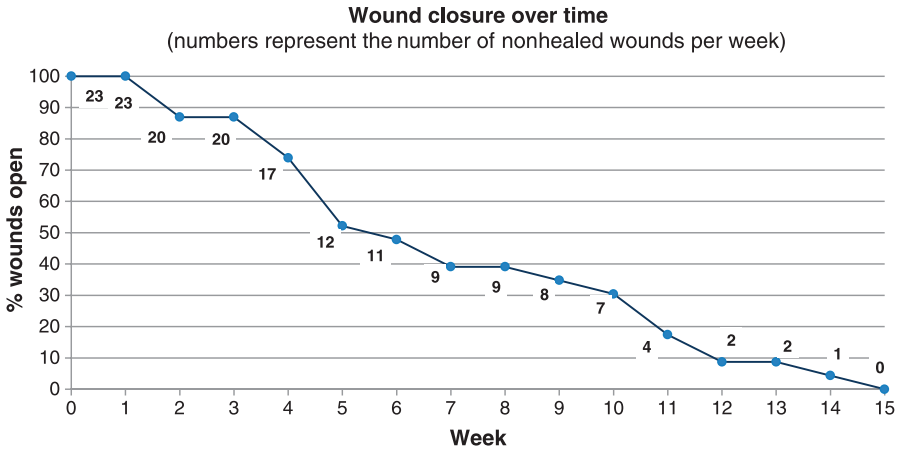
A 68-year-old man with a 20-year history of venous stasis and recurrent venous ulceration presented with a venous ulcer on the right medial malleolus. The patient was obese with history negative for diabetes and vascular disease. His ankle-brachial index was 0.93 on the left and 0.90 on the right. He had a history of bilateral vein stripping, used compression, and had been evaluated for subfascial ligation of perforators, but declined the operation. The patient returned to the clinic every 8 to 9 months with recurrent ulceration despite adequate stocking compression (30–40 mm Hg). This venous ulcer had been present for 7 months despite treatment and compression. The wound had previously been treated unsuccessfully with bilayered, bioengineered skin substitute (3 times)

Table 2.

PATIENT DEMOGRAPHICS

n	Patient/Wound ID	Baseline Area at Initial OCM Dressing Application, cm^2	Duration of OCM Dressing Treatment, wk	Wound Size End of OCM Dressing Treatment, cm^2	Healing Rate During OCM Dressing, cm^2/wk	Wound Size Reduction at Closure or 12 wk, Whichever Is Sooner, %
1	3	3.0	7	0.0	0.28	100
2	4	0.7	4	0.0	0.18	100
3	5A	4.4	9	0.0	0.41	100
4	5B	0.7	5	0.0	0.09	100
5	6A	0.6	11	0.0	0.06	100
6	6B	18.6	11	0.0	2.04	100
7	7	0.5	5	0.0	0.12	100
8	8A	0.8	2	0.0	0.41	100
9	8B	0.2	2	0.0	0.09	100
10	9A	0.8	5	0.0	0.09	100
11	9B	4.2	11	0.0	0.38	100
12	10A	0.3	4	0.06	0.06	100
13	10B	1.7	15	0.0	0.09	51.5
14	11	23.4	2	0.0	11.70	100
15	12A	1.0	5	0.0	0.21	100
16	12B	0.3	12	0.0	−0.11	100
17	12C	9.3	14	0.0	0.98	100
18	12D	0.5	5	0.0	−0.13	100
19	13	5.0	12	0.0	0.46	100
20	14A	5.7	4	0.0	1.82	100
21	14B	1.8	7	0.0	0.26	100
22	15	0.8	6	0.0	0.10	100
23	16	0.8	10	0.0	0.07	100
Average		3.7	7.3		0.9	97.9
SD		6.0	4.0		2.4	10.1
Range		0.2–23.4	2–15		−0.13 to 11.7	51.5–100

Figure 2.
NUMBER OF OPEN WOUNDS BY WEEK

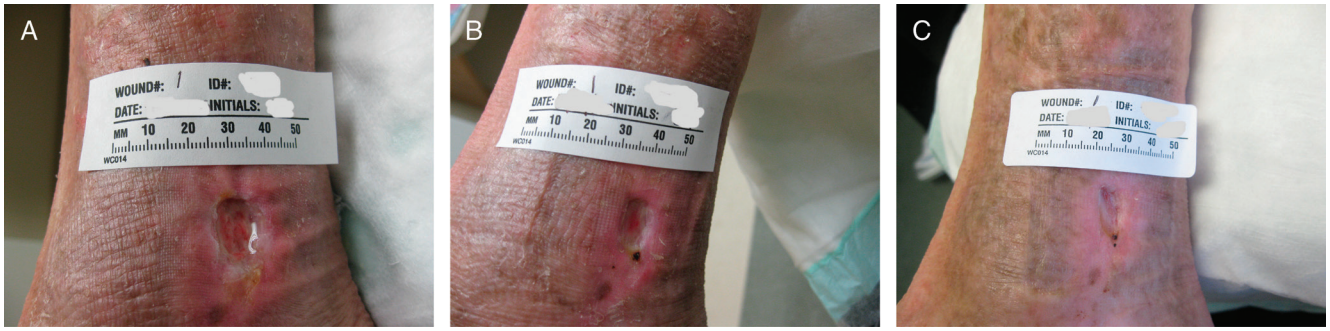


and a collagen matrix graft. Following good wound bed preparation, a CECM dressing was applied (Figure 3A). After 5 applications of CECM dressings, the wound was considerably decreased in size and re-epithelializing from the wound edges (Figure 3B). At 12 weeks, the ulcer was closed (Figure 3C).

DISCUSSION

The positive effects of CECM dressings in treating VLUs were demonstrated in this case series through a high percentage of wounds that were closed within 12 weeks (22/23; 95.7%). Larger, prospective studies report lower percentage rates of wound closure with other collagen dressings at 12 weeks. In 1 interim analysis of 84 VLUs, healing rate at 12 weeks was 71% with pig small-intestine submucosa and 46% with standard care.[29] In a different study, results at the end of the 12-week treatment period showed that healing occurred in 55% (34/62) of patients who received small-intestine submucosa wound matrix plus standard care versus 34% (20/58) of patients who received compression only (P = .0196).[30]

Figure 3A–C.
VENOUS ULCER CASE
A, DAY 0
B, WEEK 5
C, WEEK 12



Chronic, edematous venous leg ulcer with raised wound edges after 7 months of advanced wound care, including 3 applications of bilayered bioengineered skin substitute and a collagen matrix graft. Following good wound bed preparation, CECM dressing is applied.

In a study of VLUs, a total of 15 of 37 ulcers (41%) treated with collagen and oxidized regenerated cellulose healed in 12 weeks, versus 11 of 36 (31%) with Adaptic (Medline, Mundelein, Illinois).[18]

The calculated closure rate of 0.88 cm^2/wk may have been skewed with inclusion of wound 11, which displayed a rapid healing response. One week prior to CECM initiation, wound 11 measured 41.0 cm^2, and at first CECM application, the wound measured 23.4 cm^2. After 2 weeks of CECM dressings, the wound was completely closed. Excluding wound 11 from the data set produced an average healing rate of 0.44 cm^2, a rate that may be more representative of the study population.

Although compression wrap and dressing cover were changed twice per week during the study period for frequent wound observation, CECM dressings may be used up to 7 days, and compression wrap change frequency would typically be reduced to once weekly (in tandem with CECM dressing changes). Compared with other collagen dressings requiring at least twice-weekly application, the once-weekly application of CECM dressings saves healthcare system dollars in terms of reduced facility fees, material costs, and home nursing visits. Although the second weekly visit is a nursing visit versus a physician visit, it still requires the collagen, a 2- or 4-layer wrap, and the nurse's time. Based on average facility fees the investigators' institution billed during the study period, negating a midweek visit to the clinic for the purpose of changing the collagen dressing could yield a per-patient healthcare cost savings of up to $233.50 per week.

Favorable healing rates of CECM dressings may be related to the biomaterial's intact, nonreconstituted matrix. Structural studies have shown that CECM biomaterial is relatively strong and elastic and retains the complex collagen architecture of native tissue ECM.[31,32] Structural components include elastin, fibronectin, and glycosaminoglycans.[32] The CECM has been shown to retain secondary ECM-associated molecules, including fibroblast growth factor 2, heparin sulfate, and hyaluronic acid, as well as remnant basement membrane components associated with forestomach luminal surface and endothelial basement membranes.[32]

High levels of various MMPs are consistently reported in chronic wounds.[33,34] These proteases sequentially break down native extracellular matrices, causing a weakened molecular environment in the wound because of the damaged essential proteins for healing. Specifically, in a study of fluids and tissues of healing and nonhealing ulcers, Nwomeh et al[35] found that neutrophil-derived MMP-8 is the predominant collagenase present in normal healing wounds; results of that study suggest that overexpression and activation of collagenase MMP-8 is likely involved in the pathogenesis of nonhealing chronic ulcers.[35]

The CECM biomaterial appears to have an effect on MMP levels.[27] In a scientific solid-state assay study, Negron et al[27] showed that in the presence of intact CECM, residual activity of MMP-8 was reduced relative to untreated control at all time points and displayed a decrease in activity over time. In the same study, extracts of CECM were shown to inhibit a broad spectrum of excess MMPs, particularly collagenases, gelatinases, and neutrophil elastases.[27]

In the investigators' experience, CECM dressing technology has several advantages in practice. The matrix dressing does not require fixation and can be applied by any clinician in any care setting or by patients at home. It is a relatively large, thick, dense material that stabilizes easily over the wound. Generally, payer plans reimburse for advanced wound care matrices over a VLU only after the VLU has failed to adequately respond to 2 months of conservative treatment with compression therapy alone.[36,37] This ovine CECM dressing differs from that model as it is classified for reimbursement as a collagen dressing as opposed to an advanced wound care matrix dressing. As such, it is relatively inexpensive ($10–$12 each) and can be applied from the initial visit.

Investigators in the authors' clinic have switched to the CECM dressing as the standard venous ulcer dressing under compression because of its versatility, relatively low cost, and perceived effectiveness. Use of this dressing has reduced clinic applications of collagen dressings by 50%, and because this matrix collagen dressing is priced at the low end of collagen dressings, expenditure per collagen dressing has been reduced at the authors' clinic.

Because this advanced ECM dressing can be initiated during what is typically considered the 8-week timeframe of conservative treatment, based on local coverage determination policy, clinicians and patients can get a head start in wound healing with this dressing. Since the conclusion of the study, overall faster wound healing times have been observed, compared with prior treatment regimens. Use of this CECM dressing in clinic has reduced the number of outlier ulcers, that is, ulcers that extend beyond a 12-week healing window. Patients prefer CECM dressings compared with previous collagen dressings because of reduced dressing change frequency, perceived faster healing, and fewer out-of-pocket expenses for dressings. Reduced dressing application frequency may improve patient compliance with therapy by minimizing transport and time inconveniences related to clinic visits.

Indications for CECM dressings are listed in Table 3. According to manufacturer recommendations, CECM dressings are not for infected wounds or full-thickness burns and should not be used on patients with known sensitivity to ovine material. Precautions should be taken in cases of acute inflammation and excessive exudate or bleeding.

To date, the authors believe this is the first case series evaluating the use of CECM exclusively in VLUs. Liden and May[38] evaluated the matrix dressing in a series of 19 patients with 24 wounds of various etiologies, including venous, diabetic, and

Table 3.

INDICATIONS FOR OCM DRESSINGS

Pressure ulcers
Venous ulcers
Diabetic ulcers
Chronic vascular ulcers
Tunneled/undermined wounds
Surgical wounds (donor sites, grafts, post–Mohs surgery, post–laser surgery, podiatric, and wound dehiscence)
Traumatic wounds (abrasions, lacerations, partial- and full-thickness burns, and skin tears)
Draining wounds

incisional wounds.[38] The authors reported 50% of wounds closed at 12 weeks; average surface area reduction of all wounds at 12 weeks was 73.4%.[38]

CONCLUSIONS

Preliminary results of this retrospective data analysis suggest that the use of CECM dressings in VLUs may lead to improved healing, as well as potential cost savings. This study, however, has all of the limitations of a retrospective, nonrandomized, noncontrolled study. Because all wounds were treated with CECM dressings, it is not possible from the data to understand the full impact of CECM dressings versus alternative treatments. In addition, there could be a carryover effect for those who were initially treated with other dressings at baseline before crossing over to CECM dressing treatment. Wound duration and prior treatments were not considered in the data, potentially confounding study results. Investigator bias may also have confounded the results of this study with respect to wound selection and, in some cases, timing of switchover to CECM dressings.

Large, prospective, controlled trials are needed to help delineate the effectiveness of this new CECM dressing in treating VLUs and other wound types. In particular, a randomized, prospective study of consecutive VLU patients treated with compression and CECM dressings versus cellulose collagen dressings (12–16 weeks) could provide needed comparative evidence, as well as enhanced validity and generalizability of study results. A priori power analysis should be used in future CECM dressing studies to accurately estimate sufficient sample size to achieve adequate power. ●

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