Randomized Controlled Trial Comparing Collagen/Oxidized Regenerated Cellulose/Silver to Standard of Care in the Management of Venous Leg Ulcers

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ABSTRACT

OBJECTIVE: To assess healing outcomes in venous leg ulcers (VLUs) treated with a combination of collagen, oxidized regenerated cellulose, and silver in conjunction with standard of care (SOC; intervention group) compared with SOC alone (control group). Standard of care included ADAPTIC nonadhering dressing (Acelity, San Antonio, Texas) and compression.

DESIGN AND SETTING: Randomized controlled trial that followed patients in 3 US facilities for 12 weeks or until complete healing.

PATIENTS AND INTERVENTION: Forty-nine patients with VLUs were randomized to either the intervention group (n = 22) or the control group (n = 27).

MAIN OUTCOME MEASURE: Wound healing over 12 weeks.

MAIN RESULTS: Intent-to-treat analysis showed a mean percentage wound area reduction at 12 weeks of 85.6% (SD, 28.6%) for the intervention group and 72.5% (SD, 77.8%) for the control group. There was a higher healing rate in the intervention group compared with patients who received SOC only at both week 4 (23% vs 11%) and week 12 (64% vs 59%). There were no adverse events related to the study therapy.

CONCLUSIONS: Although the results were not significant, there was a trend toward faster healing in the intervention group. The results of this study indicate that collagen/oxidized regenerated cellulose/silver is a suitable and safe adjunctive intervention for use with SOC to manage VLUs.

KEYWORDS: ADAPTIC, adjunctive intervention, collagen, multilayer compression, oxidized regenerated cellulose, silver, venous leg ulcers

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INTRODUCTION

Venous leg ulcers (VLUs) are the most common chronic wounds of the lower limbs, accounting for up to 80% of lower leg ulcers[1] and affecting between 600,000 and 2.5 million individuals each year in the United States.[2–4] These ulcers are often slow to heal; 35% to 50% remain unhealed after 6 months,[5–7] up to 20% will not heal in 2 years,[8] and recurrence is common (72% of patients).[9] In addition to causing great pain and discomfort, patients are burdened with reduced quality of life.[10] The economic burden is high; 2 million working days are lost each year to VLUs, and the annual cost to the US healthcare system is approximately $2.5 billion to $3.5 billion.[11]

Multilayer compression is the standard of care (SOC) for VLUs. However, complete healing may still take months. A literature review of compression found that healing rates were 30% to 60% at 24 weeks and 70% to 85% at 1 year.[12] The Association for the Advancement of Wound Care recommends the use of adjunct therapies with SOC if progress in healing is not made within 30 days.[13]

One recommended therapy is a combination of collagen and oxidized regenerated cellulose (ORC). A randomized controlled trial (RCT) by Vin et al[14] showed a significant reduction in wound area in VLUs treated with collagen/ORC plus compression compared with compression alone. In the collagen/ORC group, the average decrease in wound size was 54.4% (median decrease, 82.4%) compared with 36.5% (median decrease, 44.6%) in the compression group.[14] Additional RCTs have shown significant benefits of collagen/ORC over control in diabetic foot ulcers and pressure injuries.[15–18]

This study evaluated the healing outcomes of VLUs treated with collagen/ORC/silver and SOC compared with SOC alone.

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Collagen/ORC/silver is a bioresorbable, open-pored, freeze-dried hexagonal pad composed of collagen (55%), ORC (44%), and silver-ORC (1%). This dressing combines the benefits of collagen/ORC (as outlined previously) with the antimicrobial properties of silver. In vitro studies have shown that this combination shows antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa.*[19] However, unlike some other silver dressings, collagen/ORC/silver is not detrimental to cell growth when tested in vitro.[19] Laboratory tests have also shown that it can reduce inflammatory protease activity[20]; this may be beneficial to wound healing as increased levels of inflammatory proteases have been associated with nonhealing wounds.[21]

The primary end point was the percentage reduction in wound area at 12 weeks. Wound area was measured using photographic digital planimetry. Secondary outcomes were based on the proportion of wounds healed (100% wound closure) during the 12-week study. In addition, pain was assessed during dressing removals, and adverse events were monitored. Clinical opinion on the ease of application for collagen/ORC/silver was also assessed using a numerical rating scale.

METHODS

This was a randomized, prospective, open-label, multicenter, comparative study conducted across 3 US facilities, including a wound clinic in Pennsylvania and 2 podiatry offices in Florida. The trial was registered at clinicaltrials.gov (NCT00235209).

Subjects were randomized on a 1:1 basis to either collagen/ORC/silver and SOC (compression and ADAPTIC [Acelity, San Antonio, Texas], intervention group) or SOC alone (control group). ADAPTIC is a primary dressing made of knitted cellulose acetate fabric and impregnated with a specially formulated petrolatum emulsion. It is designed to prevent the dressing from adhering to the wound. All subjects in both groups received Dynaflex multilayer compression (Johnson & Johnson Wound Management World Wide, Somerville, New Jersey). Inclusion and exclusion criteria are detailed in Table 1.

After informed consent was obtained via a form, subjects returned for an initial visit for screening assessments and evaluations that included pain assessment, ankle-brachial index, leg diameter measurement, baseline photograph of study wound, wound debridement, wound biopsy, blood sample, and recording of medical history and concomitant medications. All wounds were treated with ADAPTIC and compression therapy between the screening and baseline visit. Subjects returned for the first interim visit to have their dressings changed, wound evaluated, and debridement performed as necessary after 3 to 4 days.

Subjects returned for their baseline visit at least 7 days after the screening visit, once the laboratory analysis was complete. At this time, adverse event collection began, the final evaluation of eligibility took place, and subjects were randomized to either the intervention or control group.

Table 1.

INCLUSION, EXCLUSION, AND WITHDRAWAL CRITERIA FOR ENROLLING SUBJECTS

Inclusion criteria
Age ≥18 y with VLU that has been open continuously for >1 but <18 mo
Evidence of venous insufficiency documented by venous duplex scanning or impedance plethysmography within the past 6 mo
VLU area >3 cm^2 but <25 cm^2
Used prescribed compression for ≥7 d immediately prior to randomization, but not >14 d
For female subjects, a negative pregnancy test and willingness to practice an approved form of contraception throughout the study
Exclusion and withdrawal criteria
Study wound below malleolus or above popliteal fossa
Study wound treated with becaplermin or any other topical recombinant therapy within 30 d prior to study
Study wound treated with a skin substitute or an autologous growth factor at any time
A surgical procedure to treat venous or arterial disease of the affected limb within 90 d prior to the study
Evidence of significant arterial insufficiency (ABI <0.8)
Clinical evidence of active infection at wound site, active vasculitis, cellulitis, or collagen vascular disease
Participated in a clinical trial of an investigational agent within 30 d prior to this study
Significant acute or chronic diseases that were not adequately controlled
Diabetes mellitus with a hemoglobin A1c >10%
Active skin disease, such as psoriasis, which could impair ability to assess study wound
Allergic to the study components
Required concomitant use of pentoxifylline or clopidogrel bisulfate
Study wound debrided using enzymes within 7 d prior to first intervention visit
Required use of systemic steroids or immunosuppressive or cytotoxic compounds during the study or received low-dose steroid therapy for >5 d within the past year
Expected to undergo hyperbaric oxygen therapy during the study

Abbreviations: ABI, ankle-brachial index; VLU, venous leg ulcer.

Subjects returned twice weekly for dressing changes. Wound evaluations, photographs of the study wounds, and perimeter tracings were obtained during the first visit of each week. Wound area was measured during each interim and weekly visit. Pain was assessed during dressing removals using the Wong-Baker FACES scale. Following randomization, therapy continued for up to 12 weeks or until complete healing (100% wound closure) was achieved.

Randomization was used to avoid bias in the assignment of subjects, to increase the likelihood that known and unknown patient attributes were evenly balanced, and to enhance the validity of statistical comparisons across intervention groups. The sponsor's Medical Affairs Department generated the randomization codes and prepared the randomization envelopes. Randomization envelopes were opened in consecutive order, using the lowest number available for each incoming subject.

Intent-to-treat (ITT) analysis was used to analyze both the primary and secondary objectives and consisted of all subjects who received the allocated therapy following randomization and

had at least 1 postrandomization measurement of the primary effectiveness parameter. Per protocol, analysis was conducted on all subjects who met inclusion and exclusion criteria, had sufficient wound area at baseline, received a study therapy, and had data regarding the primary end point at week 12. No formal sample size calculation was performed, but data from 49 subjects were considered sufficient to evaluate trends regarding the effect of the respective dressings on the reduction in wound area.

All statistical analysis was performed using SPSS PASW 19 (SPSS Inc, Chicago, Illinois). For the ITT population, missing data were imputed using the last observation carried forward technique. Fisher exact or χ^2 test was used to compare the proportion of wounds closed between the 2 groups during the 12-week study period. Analysis of reduction of wound area from baseline to 12 weeks was conducted using the Mann-Whitney *U* test. All subjects who received an intervention were included in the safety evaluation. The proportion of subjects with adverse events was summarized by group and compared using the Fisher exact test.

RESULTS

A total of 49 patients with VLUs were randomized to either the intervention group (n = 22) or the control group (n = 27) between November 2004 and December 2005. Each center enrolled between 11 and 28 subjects. The 2 groups were comparable with respect to their demographic characteristics (Table 2). The mean wound size and VLU duration in the intervention group were 6.9 cm^2 and 4.3 months, respectively, compared with a mean of 5.6 cm^2 and 5.1 months in the control group. In the intervention group, 9% of participants (2/22) did not complete the study: 1 was lost to follow-up, and 1 chose to withdraw. In the control group, 11% (3/27) of participants did not complete the study: 2 subjects died of severe adverse events (unrelated to the study interventions), and 1 chose to withdraw.

All subjects received the intended interventions and had at least 1 postrandomization measurement on wound area reduction. Therefore, the ITT analysis included all 49 subjects. Per protocol, analysis was conducted on subjects who met inclusion and exclusion criteria, had sufficient wound area at baseline, received a study therapy, and had data regarding the primary end point at week 12; 43 subjects were included in the per protocol data set.

ITT Analysis

At week 4, there was a trend toward an improved rate of healing in the intervention group compared with the control group, with healing defined as 100% wound closure. The percentage of wounds that had healed by week 4 of the study was 23% (5/22) in the intervention group and 11% (3/27) in the control group (Figure).

Table 2.

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS FOR EACH GROUP

Demographic Data	Intervention Group (n = 22)	Control Group (n = 27)
Gender, %		
Male	72.7	55.6
Female	27.3	44.4
Age, y		
Mean (SD)	62.0 (10.30)	63.1 (17.14)
Range	42–90	24–90
Height, cm		
Mean (SD)	169.7 (10.78)	172.3 (7.40)
Weight, kg		
Mean (SD)	98.3 (29.51)	92.1 (17.10)
Wound size, cm^2		
<3	1	4
3–10	17	23
>10	4	2
Mean (SD)	6.9 (4.14)	5.6 (3.04)
Ulcer duration, mo		
1–6	17	19
6–12	3	7
≥12	2	3
Mean (SD)	4.3 (3.41)	5.1 (4.31)
Ankle-brachial index		
Mean (SD)	0.93 (0.22)	0.98 (0.13)

Note: There were no significant differences between the intervention group and control group at baseline; $P < .05$ for the comparison between groups.

Overall healing rates were good in both groups; 64% (14/22) of wounds from the intervention group and 59% (16/27) from the control group healed at 12 weeks (Figure). The mean percentage of wound area reduction at 12 weeks was 85.6% (SD, 28.6%) for the intervention group and 72.5% (SD, 77.8%) for the control group. There were no significant differences in these data. The same trend of increased healing in the intervention group was seen in the per-protocol results analysis.

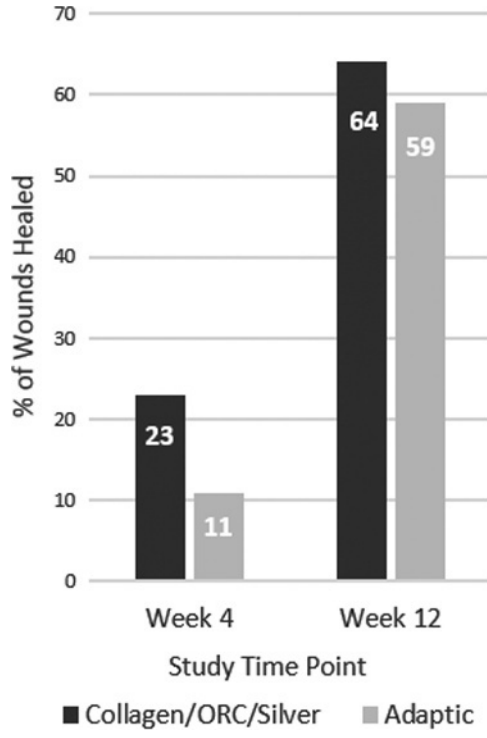
Pain Scores

All interventions were well tolerated, and pain scores were low in both groups throughout the study. The distribution of pain scores across the Wong-Baker scale at week 12/final visit, however, revealed slightly higher pain scores among the intervention group than among the control group.

Clinician Opinion

Investigators assessed each intervention for conformity to the wound, ease of application and removal, ability to maintain a moist wound bed, healing expectations, and the likelihood they would use the product again or recommend its use. The score was based on a scale of 1 to 10, with 10 being the most favorable score. The investigator assessment of scores was higher in the intervention group (mean, 8.81 [SD, 0.90]; range, 6.00–10.00 of

Figure.
PERCENTAGE OF WOUNDS TO ACHIEVE COMPLETE HEALING IN EACH GROUP AT WEEKS 4 AND 12 OF THE STUDY



147 points) than in the control group (mean, 6.71 [SD, 1.71]; range, 1.00–10.00 of 182 points) for all of the intervention characteristics at week 4.

At week 12, scores remained favorable for the intervention group (mean, 8.82 [SD, 0.89]; range, 6.00–10.00 of 133 points) over the control group (mean, 7.75 [SD, 1.74]; range, 2.00–10.00 of 147 points). For most of the characteristics, the observed scores for the intervention group were 8 or more and 8 or less for the control group (≤7 or less for some characteristics) at weeks 4 and 12.

Safety and Adverse Events

There were no adverse events related to the study therapies. The total number of adverse events reported was 15: there were 5 in the intervention group and 10 in the control group. There was no significant difference in the number of subjects reporting at least 1 adverse event in the intervention group (14% of subjects) compared with the control group (26% of subjects), $P = .478$. No inferential statistical analysis was performed, because the adverse event incidence was low.

DISCUSSION

There was a trend for increased healing rates and shorter mean time to healing in the intervention group compared with the control group, although (as expected with so few participants) no significant differences were seen. During the first 4 weeks, the intervention group had a greater healing trajectory compared with the control group. However, after that time, there was no change. This indicates that there was likely a decrease in proteases during that time frame until the wound was in balance. Sequential therapy after the 4 weeks may have continued the positive healing trend. Both study interventions were well tolerated, with no adverse events related to either collagen/ORC/silver or SOC.

This study adds to the existing body of evidence supporting the use of collagen/ORC/silver. Collagen/ORC/silver fares better than does collagen/ORC. The mean percentages of wound area reduction for the intervention in this study were 85.6% and 72.5% for SOC. In contrast, the collagen/ORC group in Vin et al[14] had an average decrease of 54.4% compared with 36.5% in the control.

In 2008, Lanzara et al[22] published an RCT showing that VLUs treated with collagen/ORC/silver and compression were 4 times more likely to heal than when treated with moist wound healing and compression (odds ratio, 4.3; $P = .04$). In addition, Gottrup et al[23] showed that significantly more diabetic foot ulcers reached the surrogate end point of 50% wound area reduction by 4 weeks when treated with collagen/ORC/silver and off-loading compared with moist wound healing and off-loading.

Although no health economic data were collected during this study, the trend toward improved healing in the intervention group may suggest that this is a more cost-effective intervention. This theory is supported by Snyder et al,[24] who carried out a retrospective economic analysis of lower-extremity wound management in the home care setting. The study found that the use of collagen/ORC and collagen/ORC/silver reduced overall healthcare costs and led to increased healing rates compared with saline-soaked gauze.[24] The average cost of 2 months' care with collagen/ORC and collagen/ORC/silver was $2,145, and 95% of wounds healed, compared with an average cost of $7,350 and 7.2% wound healing in the saline-soaked gauze group.

Clinical studies often use a run-in period to exclude the wounds that are on a healing trajectory after a short period of good standard care. This is to ensure that all wounds entering the study are on a nonhealing trajectory. This is of particular note for collagen/ORC/silver therapy, which often is used only if SOC does not work. The results of this study indicate that a run-in period may have been beneficial to this study. Both groups showed good healing rates throughout the study, with the majority of wounds decreasing in wound area between the screening visit and baseline, when only SOC was used. This suggests that when patients were entered into the study and given a high SOC the healing

rates increased. Therefore, the lack of a run-in period should be considered a limitation of the study design.

Another possible limitation of the study is that there was a low number of patients. While this study's sample size resulted in an adequately powered study, it would have been interesting to see the effect in a larger group; something all researchers hope for, although patient enrollment in a trial can be a challenge.

Pain scores were low in both groups throughout the study. Assessment of pain presents a difficult problem in wound care because it depends largely on the individual experiencing it. Pain is often underreported and may not be adequately addressed by providers. Many patients do not openly discuss pain, and cultural differences can contribute to large variations in experience, expression, and reporting of pain.[25] Given the multifaceted and subjective nature of pain, pain scales fall short on objectively quantifying the experience of pain. For instance, the Wong-Baker FACES scale is an ordinal scale that consists of a limited number of categorical responses. Moreover, it prompts patients to report acute pain rather than chronic pain. Future studies should conduct a more thorough evaluation of pain origin and assess behavioral signs of stress and anxiety in addition to using a validated pain scale.

Overall, in terms of conformity to the wound, ease of application and removal, ability to maintain a moist wound bed, healing expectations, and likelihood to use the product again or recommend its use, the clinicians favored collagen/ORC/silver compared with the SOC.

CONCLUSIONS

While the results from this study did not show statistical significance, they are clinically significant. This study has shown that both collagen/ORC/silver and ADAPTIC are suitable adjunctive therapies for use with compression in the management of VLUs. Despite the limitations of the study, results showed a trend toward increased rates of healing and shorter healing time in the intervention group compared with the control. ●

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