Equine Pericardium Collagen Wound Dressing in the Treatment of the Neuropathic Diabetic Foot Wound

A Pilot Study

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Background: Treatment of diabetic foot wounds remains a major health-care issue, with diabetic foot ulcers representing the most common causal pathway to lower-extremity amputation. Although several investigations have examined topical collagen-based dressings, none have specifically looked at equine pericardium. We, therefore, evaluated the effect of the equine pericardium dressing on neuropathic foot wounds.

Methods: Twenty-three consecutive patients with 34 neuropathic foot wounds were evaluated as part of a pilot study. An equine pericardium dressing was applied in a standard manner, and the patients followed a standard postapplication treatment protocol. Changes in wound size were recorded when the equine dressing was removed and 4 and 12 weeks after application. Patients underwent dressing changes every 3 to 4 days until healed or for 12 weeks.

Results: Thirty-two wounds in 22 patients were prospectively available for evaluation. On enrollment, the median wound size was 299 mm^2. When the equine material was removed (mean, 2.9 weeks), 30 of the wounds (94%) had improved, with a median size of 115 mm^2 and an average reduction in size of 44.3% ($P < .0001$). At 4 weeks, the average decrease in wound size was 52.3% ($P < .0001$). At 12 weeks, 15 wounds (47%) had healed.

Conclusions: This first report of equine pericardium used to treat neuropathic foot ulcerations demonstrates that the equine pericardium dressing is a safe and beneficial treatment for neuropathic wounds. (J Am Podiatr Med Assoc 99(4): 301-305, 2009)

Treatment of diabetic foot wounds remains a major health-care issue,[1, 2] with diabetic foot ulcers representing the most common causal pathway to lower-extremity amputation.[3] Current treatment of neuropathic ulcerations focuses on control of metabolic problems associated with the disease process, reduction of plantar pressure, and creation of a wound environment that is consistent with healing.[4] Topical biological wound covers have gained in popularity as a means of expediting healing.[5-13]

Advances in collagen-based wound coverings come from a multitude of sources, including neonatal foreskin, swine and bovine tissue, and, recently, equine pericardium (Unite Biomatrix Wound Dressing; Pegasus Biologics Inc, Irvine, California). The product is sterilized in a unique manner that maintains its collagen cross-linking, resulting in strength and inherent resistance to enzymatic degradation.[12, 14]

This is the first report, to our knowledge, of equine pericardium dressing used in the treatment of neuropathic foot ulcerations. Although several investigations have examined topical collagen-based dressings, none have specifically looked at equine pericardium. The objective of this investigation was to evaluate the response of diabetic neuropathic wounds to treatment with equine pericardium dressing.

Methods

Twenty-three patients with 34 neuropathic foot wounds were prospectively evaluated. Patients were included

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if they demonstrated a neuropathic foot wound (neuropathy is defined as an absent protective sensation via the Semmes-Weinstein monofilament)[15] of at least 4 weeks' duration and agreed to visit the clinic for regular follow-up examinations. All of the wounds had failed to heal despite adherence to a standard wound treatment protocol under the authors' supervision, and they were free of any active infections as judged by clinical examination. Pedal pulses were evaluated on admission to the study group, with peripheral arterial disease defined as lack of at least one palpable pedal pulse. Patient demographics are listed in Table 1. All of the patients signed a consent form to participate in the investigation.

All of the wounds were debrided of nonviable tissue, and each foot was prepared with a standard surgical preparation before application of the equine pericardium dressing. After debridement, each wound was measured and photographed. The equine pericardium dressing was prepared according to directions supplied by the manufacturer. The material used for this investigation was manually fenestrated to allow drainage of wound exudate. Before application, the equine pericardium dressing was cut to the size of the wound, with at least 5 mm of overlap, and then applied with sterile instruments. The material was anchored with a 4-0 nylon suture. To maintain complete contact with the wound bed, care was taken to maintain appropriate spacing of the suture while avoiding overtightening of the material. Any excess material was trimmed before placement of the dressing.

The postapplication dressing consisted of triple-antibiotic ointment placed directly on the equine layer, followed by a nonadherent layer and a buttress/compression dressing. In patients with excessive peripheral edema, a knee-high compression wrap was applied over the bolster dressing to foster greater graft contact while also reducing edema in the extremity. All of the patients were placed in an off-loading cast boot or healing sandal. Patients followed-up in the clinic for dressing changes every 3 to 4 days until healed or for 12 weeks (study end points). At each dressing change, the wounds were measured and were evaluated for signs of infection and for equine pericardium dressing viability. The equine pericardium dressing was maintained until the material lost contact with the wound or became completely dry (nonviable).

Change in the size of the wound when the equine pericardium dressing was removed and at 4 and 12 weeks was evaluated as a benchmark for wound healing.[16] The relationships between the percentage change in wound size at 4 weeks and three variables were evaluated: age, duration of ulcer before application, and percentage change in the ulcer when the equine pericardium dressing fell off (Table 2). The Spearman correlation statistic was used to analyze the data. The nonparametric equivalent of the t test, the Mann-Whitney test, was run to evaluate the relationship between healing at 12 weeks and patient age, ulcer duration before application, and percentage size change at equine pericardium dressing removal. The sign test, a nonparametric equivalent to the t test, was used to test for differences greater than zero when the equine pericardium dressing fell off and 4 weeks after application. All of the results were analyzed and $P < .05$ was used to indicate statistical significance.

Results

Two wounds were lost to follow-up, leaving 32 wounds for evaluation. All of these wounds reached the study end point. Ulcer size data are listed in Table 3. The size percentage difference was significantly different from zero as measured when the equine pericardium dressing was removed and 4 weeks after application. Evaluations of the wound when the equine pericardium dressing was removed demonstrated that most wounds had improved (n = 30, 94%), with only a small portion completely healed (n = 4, 13%). Slightly less than half of the wounds (n = 15; 47%) healed at 12 weeks. Patient age and ulcer duration did not differ

Table 1. Patient Demographics

Wounds (No.)	32
Patients (No.)	22
Male sex (No. [%])	17 (77)
Diabetic (No. [%])	22 (100)
Peripheral vascular disease (No. [%])	1 (5)
Smoker (No. [%])	4 (18)
Duration of ulceration (mean [mo])	10.3

Table 2. Relationships Between the Percentage Change in Wound Size at 4 Weeks and Age, Duration of Ulcer Before Application, and Percentage Change in the Ulcer when the Graft Fell Off

	Age	Ulcer Duration	Percentage Change After Graft
Correlation	0.02	0.01	0.84
P value	.91	.96	<.0001
No.	27	27	26

Table 3. Ulcer Data

Ulcer Characteristic	Mean (SD)	Median (IQR)	Range	*P* Value
Size at start (mm^2)	621.2 (1,124.3)	299 (510)	15 to 6,250	NA
Size when graft fell off (mm^2)	418.4 (828.2)	115 (494)	0 to 4,000	NA
Size change at time graft fell off (%)	−44.3 (52.0)	−39.5 (73.1)	−134.1 to 100	<.0001
Size at 4 wk (mm^2)	366.4 (819.4)	36.0 (359.0)	0 to 4,000	NA
Size change at 4 wk (%)	−52.3 (58.2)	−64.0 (65.2)	−134 to 100	<.0001
Graft duration (wk)	2.9 (0.8)	3.0 (2.0)	2 to 4	NA
Ulcer duration before graft (mo)	10.3 (9.6)	6.5 (16)	0.75 to 30	NA

Abbreviations: IQR, interquartile range; NA, not available.

Note: The sign test, a nonparametric equivalent to the *t* test, was used to test for differences greater than zero. The percentage difference fields were significantly different from zero when the sign test was used.

significantly in wounds healed at 12 weeks. Differences in percentage change in ulcer size at equine pericardium dressing removal were larger in patients with healing at 12 weeks; however, this did not reach statistical significance (Table 4). A strong positive correlation between percentage change at 4 weeks and that after the equine pericardium dressing fell off was noted. However, this strong relationship was not demonstrated between the age of the patient and the duration of the wound before application (Table 2).

Discussion

This study represents the largest patient series using a collagen dressing derived from equine pericardium in the treatment of neuropathic foot wounds. Most wounds in this series demonstrated a reduction in size when the equine pericardium dressing was removed. Statistically significant size reductions were noted when the equine pericardium dressing was removed and 4 weeks after application. In addition, the number of ulcerations that ultimately healed was similar to, or exceeded, that of other reported products.[8, 11, 13, 17, 18]

Comparison with previously published data can be useful. Although no data have been published to date with this specific collagen-type dressing, other products with a collagen base have been investigated. In the seminal investigation of Apligraf, Veves et al[11] reported a healing rate of 56% at 12-week follow-up for diabetic foot ulcerations treated with one application. Other investigations[8, 13, 17, 18] of dermal substitutes did not achieve this level of success. In the present investigation, we noted a healing rate of 47% at 12 weeks. Although this remains slightly lower than that reported by Veves et al,[11] the present wounds were considerably larger, and no randomization or exclusion was used in this pilot data collection.

OASIS Wound Matrix (Healthpoint Ltd, Fort Worth, Texas) and GraftJacket (Wright Medical Technology Inc, Arlington, Tennessee) collagen dressings have become popular,[5, 6, 8, 19-21] but no large-scale studies, such as those for Apligraf and Dermagraft,[11, 13] are available. Niezgoda et al,[8] in a randomized trial of 73 patients, demonstrated good healing (49% at 12 weeks) using OASIS. However, these results did not reach statistical significance. Several other investigators noted improvement in wound healing with the use of this product, but none focused on diabetic foot ulcerations specifically. Mostow et al[19] and later Romanelli et al[22] reported good success with the use of OASIS for venous stasis ulcerations. In multiple investigations,[5, 20, 21, 23] GraftJacket has demonstrated promising results. Winters et al,[20] in a retrospective evaluation, found good healing rates (>90%). However, their investigation was retrospective and included a myriad of wound types. In 2005, Martin et al[21] concluded that

Table 4. Analysis of 12-Week Healing

	Healed			Not Healed			
Characteristic	Mean ± SD	Median ± IQR	No.	Mean ± SD	Median ± IQR	No.	*P* Value
Age (y)	62.9 ± 10.1	58.7 ± 7.3	15	62 ± 16	55 ± 10	17	.3
Ulcer duration (mo)	9.7 ± 8.7	8 ± 9	15	10.9 ± 10.4	6 ± 21	17	.9
Change at graft removal (%)	61.3 ± 42.1	82.2 ± 63.8	13	27.3 ± 56.9	32.9 ± 28.5	13	.06

Abbreviation: IQR, interquartile range.

a regimen consisting of moist wound healing that uses an acellular matrix dressing may be a useful adjunct to appropriate diabetic foot ulcer care for deep, noninfected, nonischemic wounds. Although most clinicians treating wounds would agree with their premise of moist wound healing,[24, 25] this investigation, and in fact most of the literature involving the GraftJacket product,[5, 6, 20, 21] is of limited value because of the small sample size.

Many of the patients included in the present investigation have significant comorbidities that would have precluded them from participation in larger randomized trials, such as those published by Gentzkow et al[13] and Veves et al.[11] In both of these investigations, patients were excluded if they had a history of medical conditions considered to be a hindrance to wound healing. In addition, the average size of the wounds in the present investigation was much larger than that reported in these articles.[11, 13]

Evaluation of wound size changes is a useful tool in the determination of the effectiveness of any treatment modality. Sheehan et al[16] reported that wounds with a 53% change in size at 4 weeks have a propensity to achieve complete healing. They noted that percentage change in ulcer area after 4 weeks of treatment was a strong indication of eventual healing.[16] In the present investigation, we found an average change in wound size of just greater than 52% 4 weeks after application. This seems to suggest a positive effect of the equine pericardium material on wound healing.

With other collagen-based wound dressings, multiple applications have been advocated.[8, 13, 19] Gentzkow et al[13] demonstrated a significant change in wound healing with weekly applications, up to 8 weeks. In the present series, only one application was performed. It remains to be seen whether multiple applications of this material might offer even greater healing potential for these wounds.[13]

The present results demonstrate successful treatment of wounds when equine pericardium dressing is used, but the reasons for this success remain unclear. Perhaps the product's unique processing is the answer. Derived from equine pericardium, the tissue is inherently strong and undergoes novel processing methods. After decellularization, the tissue is stabilized by a process called *UltiFix*,[14] which allows the tissue to be stabilized in a nontoxic way. During this process, the rate of collagen cross-linking is controlled. As a result, the product demonstrates fewer breakdowns secondary to enzymatic degradation, as is often seen in chronic wounds, while maintaining strength and flexibility. The result is a moist wound environment that is resistant to enzymatic degradation and that is strong enough to resist high plantar pressures.

The inherent strength of pericardium combined with a resistance to enzymatic degradation perhaps explains this success. Further testing is needed to determine whether these results can be achieved on a large scale. This study represents pilot data that demonstrate a safe and effective treatment for neuropathic foot wounds with the potential for speedier healing than products previously reported.

Conclusions

We present the first report, to our knowledge, of the use of a collagen-based wound covering derived from equine pericardium for neuropathic foot ulcers. These pilot data demonstrate that the equine pericardium dressing is a safe and beneficial treatment for neuropathic wounds. Further large-scale investigations are warranted.

Financial Disclosure: This investigation was performed with support from Pegasus Biologics Inc, including donation of material and support for statistical analysis.

Conflict of Interest: Dr. John G. Fleischli is a member of the Pegasus Biologics Inc medical advisory board.

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