Acellular Fetal Bovine Dermal Matrix in the Treatment of Nonhealing Wounds in Patients with Complex Comorbidities

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Background: In contrast to the narrow indications for living skin equivalents, extracellular matrix biomaterials are clinically used in a wide range of wound-healing applications. Given the breadth of possible uses, the goal of this study was to retrospectively compile and analyze the clinical application and effectiveness of an extracellular matrix biomaterial derived from fetal bovine dermis (PriMatrix; TEI Biosciences, Boston, Massachusetts) in patients treated by a single physician and monitored postsurgically in an outpatient wound care center.

Methods: A retrospective medical record review was conducted of consecutive patients treated from January 2007 through January 2009 with meshed PriMatrix after sharp/surgical debridement and coverage with standard moist wound therapy dressings.

Results: Twenty-nine patients and 34 wounds were compiled. All of the wounds were unresponsive to conservative treatment owing to complications, including infection, exposed bone or tendon, and other comorbidities known to delay healing. Wounds included 11 diabetic ulcers, 8 venous stasis ulcers, 10 nonhealing traumatic wounds, and 5 other chronic wounds. Thirty of 34 wounds healed, with four patients lost to follow-up. Mean time to healing for diabetic foot ulcers was 105 days with an average of 2.6 PriMatrix applications. Mean time to healing for venous, traumatic, and other chronic wounds was 74 to 82 days with an average of 1.2 to 1.4 PriMatrix applications.

Conclusions: In patients with comorbidities known to delay healing, the implantation of PriMatrix promoted the healing and, ultimately, full reepithelialization of otherwise unresponsive wounds of varied etiology, including those with complications of infection or exposed bone or tendon. (J Am Podiatr Med Assoc 102(3): 233-239, 2012)

Among the therapeutic options for recalcitrant wounds, bioengineered skin tissues (eg, living skin equivalents) and extracellular matrix biomaterials (eg, acellular tissue products) offer alternatives to an autologous skin graft. Although the human living skin equivalents Apligraf (Organogenesis Inc, Canton, Massachusetts) and Dermagraft (Advanced BioHealing Inc, Westport, Connecticut) have proved to be effective in the treatment of diabetic foot ulcers and venous ulcers, their efficacy has not been established in complex wounds, such as those with exposed bone or tendon, or in patients with multiple comorbidities. Moreover, these bioengineered human skin substitutes are indicated only for wounds without tendon, muscle, joint capsule, or bone exposure because, similar to a skin graft, living skin equivalents are to be placed on tissue with strong viable vascular support.

In contrast, extracellular matrix biomaterial products, such as GraftJacket (Wright Medical Technology Inc, Arlington, Tennessee) (derived from human cadaveric dermis), Oasis Wound Matrix (Healthpoint Ltd, Fort Worth, Texas) (derived from porcine small-intestine submucosa), and PriMatrix (TEI Biosciences, Boston, Massachusetts) (derived from fetal bovine dermis) are Food and Drug Administration indicated for wounds of various etiologies, including those with factors that complicate healing, such as the presence of infection or exposed bone or tendon. Such extracellular matrix biomaterials have been reported to accelerate wound closure relative to moist wound dressings in diabetic ulcers and venous or arterial venous ulcers. However, prospective and retrospective clinical studies typically control for, or exclude, patients with complicating factors. This study specifically studied one such extracellular matrix biomaterial, PriMatrix, indicated for treating a variety of wound etiologies, including diabetic,
venous, and pressure ulcers; surgical wounds; and traumatic wounds. Although use in this wide array of indications can be a clinical benefit, published studies across this spectrum are limited. Therefore, the demographics of clinical use have not been well established, and neither has effectiveness across all indications. Consequently, the goals of this study were twofold. First, this study aimed to retrospectively compile and analyze the clinical demographics of patients and wounds treated with PriMatrix. The second goal was to investigate the effectiveness of PriMatrix across the full spectrum of treated patients.

PriMatrix is conveniently grouped with other extracellular matrix biomaterials because of similar features (eg, acellular, allogeneic, or xenogeneic origin, derived from the extracellular matrix of tissues), but these extracellular matrix biomaterials are not all equivalent. The varied starting tissues are processed using different proprietary methods that effectively remove cells but that can retain some or many components of the extracellular matrix known to affect the biological response. 19-21 Specifically, PriMatrix is an acellular dermal tissue matrix derived from fetal bovine dermis that has been processed to remove all lipids, fats, carbohydrates, and noncollagenous proteins, leaving primarily intact fetal dermal collagen fibers. 19 This fetal collagen substrate, unique to PriMatrix, is capable of binding growth factors and cells while providing a fiber architecture supportive of cell migration, proliferation, and differentiation. 19,22 Although primarily composed of type I collagen fibers similar to adult dermis, fetal dermis contains upward of a fivefold greater proportion of type III fibrillar collagen, a collagen type associated with healing and developing tissues. 19 The unique structural matrix of fetal tissues has also been identified as a contributing factor in scarless healing by altering remodeling and inflammatory signaling.23-26

Clinically, PriMatrix has been reported to heal diabetic foot ulcers and venous stasis ulcers more rapidly than does Apligraf. 27 In addition, the product has been reported to be successful in healing skin defects subsequent to traumatic skin injuries 28,29 and Mohs skin cancer 30 resection. Other researchers 31,32 have used the fetal dermal extracellular matrix to rapidly build neodermal tissue in full-thickness wounds across large surface areas that subsequently supported delayed split-thickness skin grafts to achieve primary closure, typically 7 to 10 days after PriMatrix application.

The results of this study suggest that at the author’s wound care practice, the extracellular matrix biomaterial PriMatrix is used primarily on classically difficult-to-heal wounds in predominantly elderly, chronically ill patients with complex comorbidities. The results show that PriMatrix is effective in the healing of chronic nonhealing wounds that failed conventional treatment and were often complicated by wound infection and exposed bone or tendon in this difficult patient population. The report of this real-world experience establishes baseline clinical outcomes for PriMatrix-treated wounds that are valuable for setting treatment expectations for differing wound types.

Methods

Institutional review board approval was obtained from Western IRB, Olympia, Washington, to conduct a retrospective medical record review of my clinical cases with PriMatrix treatment. The inclusion criteria consisted of failure of conventional treatment and subsequent treatment with the acellular dermal matrix PriMatrix, with clinical follow-up conducted at this practice between January 1, 2007, and January 1, 2009. No specific exclusion criteria were used. For example, patients were not excluded from the study if they received concomitant treatment with other modalities, such as vascular interventions, topical antibiotics, or other advanced wound therapies.

Before PriMatrix application, standard methods were used to prepare wound beds to ensure that the wound was free of debris and necrotic tissue. Such preparation included initial sharp/surgical debridement of the wound until bleeding to ensure that the wound edges contained viable tissue. PriMatrix was rehydrated in room temperature 0.9% sterile saline (typically for <1 min) and was meshed (1:1.5) or fenestrated with a No. 11 scalpel blade to allow for increased fluid drainage and better contouring to the wound. PriMatrix was then directly applied to the wound, covering the entire wound bed, and fixed in place with 3-0 degradable sutures or adhesive skin closure strips.

After PriMatrix fixation into the wound, a nonadherent dressing was applied and then was covered with secondary dressings. For low-exudate wounds, a moist wound environment was maintained by rubbing hydrogel into the nonadherent dressing, which was then covered with petrolatum gauze, followed by wet-to-dry gauze soaked in saline, and then wrapped with a flexible gauze bandage roll or a self-adherent elastic wrap. For high-exudate wounds, such as venous stasis ulcers, the nonadherent dressing was applied, covered with
absorptive layers to prevent excessive fluid buildup, and then wrapped with appropriate secondary dressings. The secondary dressing was changed on day 3 after PriMatrix application and as needed thereafter to maintain a moist, clean wound. Suture material was removed after 2 weeks. During dressing changes, if the PriMatrix appeared white or caramelized in color, the wound was left untouched until the PriMatrix was no longer visible and only red granular tissue remained (typically 2–3 weeks). At this point, saline or saline-soaked gauze was used to gently debride the wound before reapplying the meshed PriMatrix. Wounds were also treated with standard therapies specific to wound type (eg, off-loading for diabetic foot ulcers and compression for venous stasis ulcers).

The wounds were assessed weekly, with the first assessment occurring 1 week after PriMatrix application. Before the initial wound assessment, there was no disruption of the graft, wound, or primary dressing during secondary dressing changes. Once epithelialization began, the wounds were assessed twice per month until the patient was discharged.

Results

Twenty-nine patients met the inclusion criteria and had a combined 34 lower-limb wounds before initial treatment with PriMatrix. Patient characteristics of the entire population are given in Table 1. This population was predominantly female (79%) and advanced in age (mean ± SD age, 77.3 ± 11.9 years). Most patients were diagnosed as having some form of vascular problem of the lower extremities, with 24 of 29 patients (83%) having peripheral vascular disease or venous insufficiency. Close to half of the patients (48%) were being treated with anticoagulants for comorbid conditions. In this patient population, wound size varied widely from small (<1 cm²) to very large, including six wounds greater than 50 cm² in area (Table 2). Nearly half of the wounds were complicated by exposed bone or tendon. Other significant wound complications included infection (29%) and ischemia (26%). Thirty of the 34 wounds treated with PriMatrix healed. For four patients, follow-up was not possible.

The population and wound characteristic data were further categorized by wound types, which typically have different etiologies and treatments (Table 3). Eleven patients had 11 diabetic ulcers, 7 patients had 8 venous stasis ulcers, 9 patients had 10 nonhealing traumatic wounds, and 4 patients had 5 other chronic wounds. In all of the groups except the diabetic ulcer group, the mean body mass index (calculated as weight in kilograms divided by height in meters squared) was below the obese range. Patient and wound characteristics (Table 3) and the results of treatment (Table 4) are described individually in the following paragraphs for each wound type.

The mean age of patients with diabetic ulcers (70 years) was younger than that of the overall study population. Seven of 11 patients with diabetic ulcers were obese. This was the only group with a mean body mass index greater than 30 kg/m². As expected, most patients with diabetic ulcers had neuropathy. In addition, more than half of these patients were taking anticoagulants or had peripheral vascular disease or venous insufficiency. Diabetic ulcers were the most complex wounds based on greatest average wound area (39.1 cm²) and frequency of exposed bone or tendon, infection, and wound ischemia. In addition, six of the wounds were tunneling or undermining wounds. On average, diabetic ulcers required 2.6 (range, 1–8) PriMatrix applications and healed in a mean of 105 days.

Table 1. Characteristics of the 29 Patients Treated with PriMatrix

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (mean ± SD [range]) (years)</td>
<td>77.3 ± 11.9 [40–92]</td>
</tr>
<tr>
<td>Female sex (no. [%])</td>
<td>23 (79)</td>
</tr>
<tr>
<td>BMI (mean ± SD [range])</td>
<td>27.6 ± 6.1 [19.2–42.3]</td>
</tr>
<tr>
<td>PVD/VI (no. [%])</td>
<td>24 (83)</td>
</tr>
<tr>
<td>Osteomyelitis (no. [%])</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Neuropathy (no. [%])</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Immunosuppressant (no. [%])</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Anticoagulants (no. [%])</td>
<td>14 (48)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PVD/VI, peripheral vascular disease or venous insufficiency.

Patients treated for osteomyelitis before PriMatrix implantation.
Concomitant drug treatment (not prescribed as part of wound treatment).

Table 2. Characteristics of the 34 Wounds Treated with PriMatrix

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound area (mean ± SD [range]) (cm²)</td>
<td>19.6 ± 41 [0.16–280]</td>
</tr>
<tr>
<td>Exposed bone or tendon (no. [%])</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Infection (no. [%])</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Ischemic (no. [%])</td>
<td>9 (26)</td>
</tr>
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Five of the six patients with venous stasis ulcers were women (mean age, 80 years). All of these patients had peripheral vascular disease or venous insufficiency; however, none were obese, and few had neuropathy or were taking anticoagulants. The mean wound area of 12.5 cm² was smaller than that for diabetic ulcers and nonhealing traumatic wounds. Furthermore, few of these wounds had exposed bone or tendon, infection, or wound ischemia. Venous stasis ulcers healed in a mean of 82 days with an average of 1.4 (range, 1–2) PriMatrix applications.

Patients with nonhealing traumatic wounds were all nonobese women and were the oldest among the study patients (mean age, 85 years). Slightly more than half of these patients had concomitant peripheral vascular disease or venous insufficiency, and one-third were neuropathic or were taking anticoagulants. The mean wound area was 21.8 cm². None of these wounds had exposed bone or tendon or infection, and very few had wound ischemia. Nonhealing traumatic wounds received an average of 1.2 (range, 1–2) PriMatrix applications and healed in a mean of 75 days.

All four patients with other chronic wound types (two surgical wounds and three pressure ulcers)
were women and were taking anticoagulants, and most had peripheral vascular disease or venous insufficiency. The mean wound size (1.0 cm²) was notably smaller than that of the other wounds in this study. Of the five wounds in these patients, all had exposed bone or tendon, one was infected, and none were ischemic. An average of 1.4 (range, 1–2) PriMatrix applications in these wounds resulted in a mean time to healing of 74 days.

Because no exclusion criteria were used, the accompanying use of other advanced bioengineering products or therapies was reviewed. None of the patients were treated with other advanced wound care products or negative-pressure wound therapy, except for one patient who received a piece of single-layer porcine small-intestinal submucosa during treatment and multiple patients who were treated with topical antibiotics.

Discussion

Establishing expected outcomes for a population of complex wounds of diverse etiology is challenging. Values reported for time to complete wound healing and rate of healing vary substantially depending on wound type and size, which is further complicated by the aforementioned factors known to delay healing. In addition, given the wide breadth of PriMatrix clinical uses, the treated patients and wounds for which treatment is effective have yet to be well-defined. Therefore, the goal of this study was to retrospectively compile and analyze clinical outcomes for wounds treated with PriMatrix to better understand who and what has been treated, and the effectiveness in those arenas.

In this single-center study of 29 patients and 34 wounds, four basic categories of wounds stemming from different etiologies were treated, including diabetic foot ulcers, venous leg ulcers, nonhealing wounds originally from a trauma, and other wound types (namely, nonhealing surgical wounds and pressure ulcers). Chronic nonhealing diabetic foot ulcers have been fairly well-studied and often require advanced healing modalities to expedite healing and avoid complications.33 An often-cited meta-analysis by Margolis et al34 sets some expectations for healing of diabetic neuropathic foot ulcers treated with standard wound care. In that study, 24% of diabetic neuropathic foot ulcers healed with 12 weeks of standard wound care, and 31% healed by 20 weeks. In the present study, two patients with diabetic ulcer were lost to follow-up. The other nine diabetic ulcers treated with PriMatrix, most of which were complicated by exposed bone or tendon and infection, healed in a mean of 105 days (15 weeks). Although there are numerous prospective studies15-16 investigating other products in diabetic foot ulcers, all of the patients included in this study would have been excluded from those studies owing to comorbidities or wound complications, such as tunneling or exposure of tissue below the dermis with limited vascularity.

Despite including all of the patients, the subset of patients in the present study treated for venous ulcers had similar outcomes as studies of other extracellular matrix biomaterials and bioengineered skin substitutes in venous ulcers with more stringent exclusion criteria. All seven venous ulcers (mean area, 12.5 cm²) treated with PriMatrix healed in a mean of 82 days. All but one of these patients healed within the 12-week time frame often cited in prospective studies. This compares favorably with the extracellular matrix biomaterial OASIS, where 34 of 62 patients (55%) with a mean ulcer area of 10.2 cm² healed at 12 weeks.17 In a case-matched head-to-head retrospective study of venous ulcerations, PriMatrix-treated wounds had an average healing rate of less than 12 weeks, similar to patients in this study, and was more rapid in healing than was the living skin substitute Apligraf despite larger average initial wound areas.27

In addition to use in diabetic and venous ulcers, PriMatrix is currently indicated for the management of wounds where human living skin substitutes are not, such as second-degree burns, surgical wounds, and traumatic wounds. In this study, only chronic nonhealing wounds of these etiologies were treated, including traumatic wounds, pressure ulcers, and surgical wounds. After nonhealing with conventional treatment, these wounds closed an average of 75 days after PriMatrix implantation into the wound.

An observational difference noted between PriMatrix and past investigator experience with any of the aforementioned advanced wound-healing products occurred at application and may offer a possible mechanism to explain the results. After debridement and application of PriMatrix, the porous material turned bright red, soaking up the patients’ own blood within minutes. Collagen has a strong biochemical affinity for binding growth factors and angiogenic cytokines that are present in patient plasma and is an ideal protein for cell attachment and proliferation. This ability to sequester and bind patient cells and wound-healing growth factors in a well-conserved dermal architecture may
work in concert to stimulate revascularization and dermal regeneration, particularly in areas of low vascularity that are otherwise difficult to heal, such as over exposed bone and tendon.

Although the initial costs of these biologically active materials are substantially higher than those of conventional gauze wound dressings, one must consider the health-care costs avoided with expedient closure of nonhealing wounds. Advanced wound care can be cost effective, even cost saving, by decreasing the costs associated with hospitalizations, amputations, and other surgical procedures. The direct health-care costs of managing chronic wounds, such as nursing time, hospitalization, medications, dressings, and supplies, are obvious. The benefits of avoiding wound infection or limb amputation, however, involve financial and human factors. There are indirect costs to consider, such as lost work time and productivity, decreased quality of life, physical pain, and depression.

The findings of this study must be considered in light of the inherent limitations of a small, uncontrolled, retrospective study. The small study population and absence of a control group do not allow for direct comparison of PriMatrix outcomes with those of conventional wound care or other bioengineered tissues or advanced modalities. Further evaluation of PriMatrix in prospective randomized clinical trials is recommended to more definitively assess improved clinical outcomes in healing chronic wounds.

In this series of patients with numerous comorbidities associated with healing delay, wounds of varied etiology and size healed in 10 to 15 weeks with an average of 1.2 to 2.6 PriMatrix treatments, including many classically difficult-to-heal wounds with infection or exposed bone or tendon. Successful wound closure was achieved despite complicating patient factors, including advanced age, obesity, diabetes, peripheral vascular disease or venous insufficiency, neuropathy, and concomitant use of anticoagulants. Many of the patients treated with PriMatrix in this small study were strong candidates for amputation if their wounds did not heal. By avoiding amputation, patients’ limbs were salvaged, their quality of life was maintained or improved, and the hospital costs associated with amputation and postsurgical wound care were avoided.

Conclusions

PriMatrix fetal bovine dermal matrix successfully healed wounds of varied etiology and size in patients with complex comorbidities known to delay healing. Treatment was notably successful in classically difficult-to-heal patients with infection or exposed bone or tendon.

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References


