

Use of a Lyophilized Bovine Collagen Matrix in Postoperative Wound Healing

STEVEN A. KOLENIK, III, MD, THOMAS W. MCGOVERN, MD, AND DAVID J. LEFFELL, MD

Department of Dermatology, Section of Dermatologic and Laser Surgery, Yale University School of Medicine, New Haven, Connecticut

BACKGROUND. Immediate reconstruction is the preferred approach to the management of defects following Mohs micrographic surgery. In a minority of patients, however, reconstruction is contraindicated, and a long-term biological dressing that stimulates wound healing and minimizes wound care is desirable.

OBJECTIVE. We wanted to assess the utility of a lyophilized, type I bovine collagen matrix (*SkinTemp*) in wound care and wound healing following Mohs micrographic surgery.

METHODS. Fifteen patients were treated with a bovine collagen matrix following Mohs micrographic surgery. Study wounds were evaluated for time to complete granulation, time to complete epithelialization, and adverse reactions including infection and allergy. The time to complete healing (granulation and epithelialization) for this group was compared to 15 size- and site-matched surgical defects.

RESULTS. The use of bovine collagen matrix provided more rapid wound healing than traditional second intention healing at all anatomic sites studied. The time to complete healing averaged 6.1 weeks with bovine collagen matrix versus 9.4 weeks for the control group. Use of bovine collagen matrix required an average of 3.0 dressing changes weekly compared to 7.0 changes weekly in the control group. There were no wound infections or allergic reactions to it.

CONCLUSIONS. A Type I bovine collagen matrix provided a safe, readily available alternative to traditional methods of second intention healing. It minimized wound care while reducing the time for complete healing. A larger study should be performed to confirm the results of this pilot study.

MOST SURGICAL DEFECTS created following Mohs or conventional excisional surgery are easily reapproximated with sutures,^{1,2} however, there are a minority of surgical wounds that are best managed by second intention healing.³ Although second intention healing may result in excellent final results, healing is often protracted and requires daily wound care by the patient or caregiver. The clinical challenge in these patients is to develop an ideal biological dressing that is readily available and inexpensive, speeds healing, and minimizes wound care.

Previous efforts to meet this challenge have resulted in porcine xenografts,⁴ human cadaveric allografts,⁵ a variety of keratinocyte preparations,⁶ and bovine collagen/allogeneic keratinocyte bilayers.⁷ We report our experience using a lyophilized, cross-linked matrix of Type I bovine collagen (*SkinTemp*, Biocore, Inc., Topeka, KS) in wound healing following Mohs micrographic surgery.

Presented at the American Society of Dermatologic Surgery, Hilton Head, South Carolina, May, 1995.

This study was supported by a grant from Biopore, Inc. (Topeka, KS).

Address correspondence and reprint requests to: David J. Leffell, MD, Department of Dermatology, Yale University School of Medicine, P.O. Box 208059, New Haven, CT 06520-8059.

Materials and Methods

During 1995, 15 patients with surgical defects that were created following Mohs micrographic surgery for basal cell or squamous cell carcinoma were enrolled in a clinical trial of a Type I bovine collagen matrix, used as an aid to postoperative wound healing. After complete tumor extirpation using the Mohs fresh-tissue technique, all immediate reconstructive options were considered. If both the surgeon and the patient thought that healing by second intention was the best approach, then, and only then, was the patient offered enrollment in this clinical trial. Exclusion criteria included a history of collagen vascular disease, known allergy to bovine products, or immunosuppression, including immunosuppressive therapy.

All surgical wounds were measured in 3 dimensions and photographed on day zero. *SkinTemp* was cut to fit the surgical defect, hydrated with 0.9% saline, and placed in the wound (Figure 1). The collagen matrix was then covered with antibiotic ointment, a non-adherent dressing, and paper tape. Patients were instructed to change the collagen matrix as needed, based on wound drainage and/or liquefaction and absorption of the product from the wound bed. All patients were given a diary, in which they recorded all dressing changes. Patients were seen at 1-week intervals until complete healing had occurred. All defects were photographed and measured in 3 dimensions at each patient visit, and surgical wounds were assessed for evidence of wound infection and/or allergic reactions to the collagen matrix.

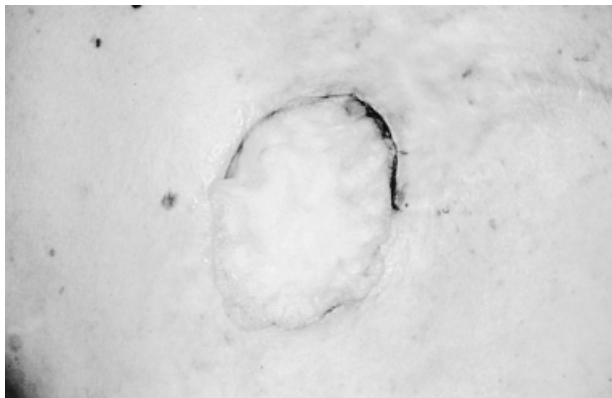


Figure 1. Appearance of hydrated bovine collagen matrix immediately after placement in wound bed.

For purposes of this study, healing was divided into two components: *complete granulation*, defined as a surgical wound in which the wound bed had granulated up to the plane of the surrounding normal epidermis, and *complete re-epithelialization*, defined as complete resurfacing of granulation tissue with epidermis.

If, at anytime during the study, a patient could tolerate and benefit from other reconstructive techniques, these were offered to the patient. If accepted, the patient was removed from the study. Patients were told to resume their normal daily activities immediately following surgery.

We compared the time to complete healing (granulation and epithelialization) in 15 size- and site-matched wounds that healed by second intention during the time period of the study. Because these were historical controls, we did not have information on time to complete granulation for the control wounds. In our institution, wound care includes daily wound tap water washing followed by application of antibiotic ointment beneath a non-adherent dressing. The only difference between treatment of the study and control patients was the collagen matrix placed in the wounds of the study patients. Patients with conditions that might delay wound healing (e.g., diabetes mellitus, immunosuppressive medications) were excluded from the study.

Results

All 15 patients (13 men, 2 women; mean age = 74.2 years) enrolled in this pilot study successfully completed it without significant side effects. All study patients were able to complete dressing changes on their own without the need for visiting nurses. There were no wound infections or allergic reactions to collagen matrix, and the product was well tolerated. Patients reported in their diaries that they changed their dressings an average of 3.0 times per week compared to the normal wound care of daily dressing changes (7.0 times per week) for control patients. No other wound

care was required. The average surgical defect measured 2.8×2.5 cm and extended to fat or fascia on the face (10), back (2), leg (2), or scalp (1) (Table 1). The average time to complete granulation with bovine collagen was 3.5 weeks, while the time to complete re-epithelialization (complete healing) was 6.1 weeks. Figures 2 A–C demonstrate complete healing of a large defect on the back by Week 6. Although we did not specifically compare study and control wounds for cosmetic appearance, we noted no striking differences in cosmesis between the 2 groups.

The control sites were evaluated only for time to complete re-epithelialization (complete healing), and this averaged 9.4 weeks for all 15 wounds (Table 2). While the collagen-matrix-treated wounds healed over 3 weeks faster and in 65% of the time it took the conventionally-treated wounds to heal, the sample size was too small to assess for statistical significance, and this is likely due to both the small sample size and patient-to-patient variability in healing times.

Discussion

Although conventional methods of reconstruction are appropriate for the vast majority of patients undergoing Mohs surgery and conventional excisional surgery, there remains a minority of patients in whom healing by second intention is necessary or preferred. Despite many attempts to create an ideal biological dressing for such wounds, second intention healing remains cumbersome and protracted for most patients, requiring daily wound care over a long period of time, especially if visiting nurses are required. Our experience with a bovine collagen matrix product reveals that it may be an excellent alternative to traditional methods of second intention healing both by minimizing daily wound care (3.0 versus 7.0 dressing changes per week in study and control patients, respectively) and by speeding the time to complete healing.

At all anatomic sites studied, the bovine collagen persisted in wounds up to 1 week without daily dressing changes, while eliciting more rapid complete healing of wounds. Collagen matrix products possess low antigenic potential and act as poor culture media for bacteria, thus allowing the material to remain safely in a wound for prolonged periods.⁸

The mechanisms by which heterologous collagen matrices assist wound healing include hemostatic, spatial, nutritional, and chemotactic effects. The three-dimensional collagen network provides an architectural scaffold for aggregation of platelets and coagulation factors to improve hemostasis.⁹ The orderly mechanical support rapidly organizes fibroblasts and newly-formed collagen fibers into a regular network.^{8,10} Denatured bovine collagen contains more fibronectin binding sites,

Table 1. Characteristics and healing times for all patients enrolled in the Type I bovine collagen matrix study. Healing time is divided into time to complete granulation and time to complete healing (with epithelialization).

Patient Number	Sex	Age	Tumor	Site	Size (cm)	Time to Complete Granulation (Weeks)	Time to Complete Healing (Weeks)
1	M	77	BCC	Face	2.0 × 2.0	3	5
2	F	75	SCC	Leg	1.4 × 1.4	5	7
3	M	85	BCC	Face	2.0 × 1.5	3	4
4	M	79	BCC	Face	2.5 × 2.0	3	4
5	M	67	SCC	Scalp	3.5 × 4.0	3	8
6	M	77	BCC	Face	2.5 × 2.0	3	5
7	M	77	BCC	Face	4.0 × 3.0	3	7
8	F	74	BCC	Back	4.7 × 4.0	4	6
9	M	76	BCC	Face	2.5 × 2.0	4	6
10	M	77	BCC	Face	2.5 × 2.5	3	6
11	M	81	BCC	Back	5.0 × 6.6	3	7
12	M	68	SCC	Leg	4.0 × 3.0	5	8
13	M	62	BCC	Face	2.0 × 1.3	3	5
14	M	62	BCC	Face	1.0 × 1.0	3	6
15	M	76	BCC	Face	1.8 × 1.0	4	7
Mean		74.2			2.8 × 2.5	3.5	6.1

and; at least in vitro, increased fibronectin binding stimulates migration of fibroblasts.¹⁰ Evidence also suggests that bovine collagen supplies some early nutritional needs of granulation tissue.⁸ Finally, the degeneration of the collagen matrix may promote fibroblast migration because collagen degradation products are chemotactic factors for stromal fibroblasts.^{8,10} Both the three-dimensional scaffold and chemotactic factors likely assist more rapid migration of epithelial cells.⁹

In a study comparing punch biopsy defects on the trunk and upper extremities, Smith et al noted several histologic differences between wounds that healed with and without a Type I bovine collagen matrix.⁹ Acute inflammatory cells were more numerous and remained longer in the wounds not treated with bovine collagen. Epithelial cells began migrating over, but not into, the bovine collagen matrix by Day 2 of healing, while the untreated sites had delayed epithelial cell mi-

gration that included cells descending into the granulation tissue as well as traveling over the surface. Hyaluronic acid and host collagen appeared more rapidly and in a more regularly oriented fashion in the bovine collagen-treated wounds.

Unlike Smith et al, Becker and co-workers found no difference in the rate of wound epithelialization when treating 111 facial defects following Mohs micrographic surgery.¹¹ However, dressings were changed only once each week, regardless of the amount of exudate. The outcome criteria were vague and subjective (favorable versus poor cosmesis), the judges were not blinded, and the study design allowed very low statistical power. The authors state that further study of heterologous collagen in second intention healing is needed because of these study limitations and because of several small reports in humans^{8,10,13} of improved healing with bovine collagen matrices.

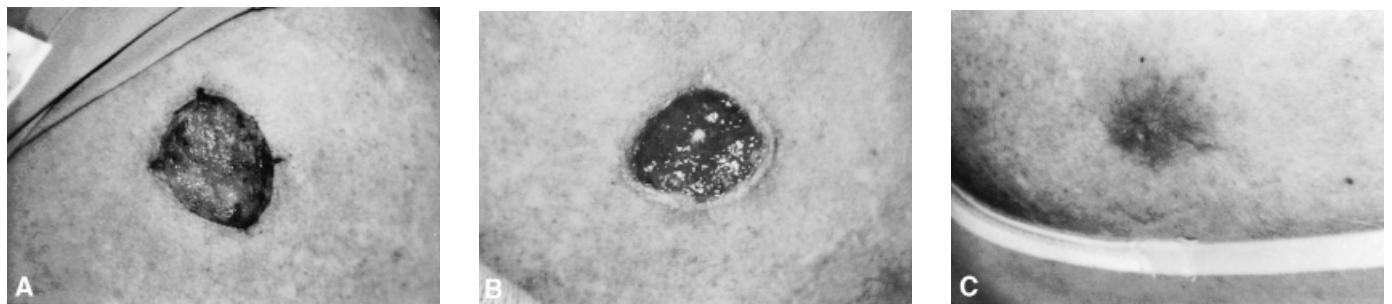


Figure 2. A) A large surgical defect of the back following Mohs surgery for a recurrent basal cell carcinoma. B) Surgical defect of the back showing good granulation tissue formation following 3 weeks of bovine collagen matrix application. C) Defect of the back showing complete healing after 6 weeks of bovine collagen matrix.

Downloaded from http://journals.lww.com/dermatologicsurgery by b2H79IKgmkstf+820f+e+hK7DCsfhw6GVIGIT
RgCHqGTrmM7Kk1qdxsXpnG3CQPSPgSjMHFEbBhBBAZB14LYQz3tkm1thvE6pXRWUJC4IOJFduuJKAWPLAPf150X01joq2U
Nm6K5Y2A1AgkCbsf/b/AaaQ on 04/09/2024

Table 2. Site and size comparison of time in weeks to complete healing (granulation and re-epithelialization) for patients treated with *SkinTemp* (Type I bovine collagen matrix) and traditional second intention healing.

	Face (n = 10)	Scalp (n = 1)	Back (n = 2)	Leg (n = 2)	All sites (n = 15)
Bovine collagen matrix	5.5	8.0	6.5	7.5	6.1
Conventional second intention	7.5	16.0	14.5	10.5	9.4

In conclusion, our study lends further evidence that a bovine collagen matrix may stimulate more rapid wound healing with minimal to no side effects and high patient satisfaction. These clinical effects are likely due to the bovine collagen's recapitulating the natural dermal collagen matrix to allow more rapid and organized hemostasis and recruitment of epithelial cells and fibroblasts to the wound. We believe that most second intention healing wounds created during Mohs micrographic surgery could benefit from such an aid as this relatively inexpensive Type I bovine collagen matrix. The weaknesses of this study are the use of historical controls and the small sample size. As there is great variation in healing time between different wounds, and because the sample size is small, these results could be due to chance alone. However, based on the results of this pilot study, we believe that a large, controlled, multicenter clinical trial of a bovine collagen matrix is warranted to better quantify its effects on wound healing.

Commentary

I have often likened the practice of medicine to a long, multi-year, uncontrolled clinical trial. At the end, physicians have learned what to do and what might be expected in a large number of situations. However, we do not know what might have happened had we done something other than what we did or had we done nothing at all.

This report is important from at least two points of view. First, the investigators recognized the importance of studying a quality-of-life issue, the duration of healing, and its attendant wound care effort. Too often, such issues which are of great importance to patients and their families are viewed by physicians as minor or trivial. This attitude is often resented by patients and families, and spoils what should have been a much-appreciated intervention. Unfortunately, because in this study the historical control patients were instructed to change their dressings

References

1. Tromovitch TA, Stegman SJ. Microscopically controlled excision of skin tumors: chemosurgery (Mohs) fresh tissue technique. Arch Dermatol 1974;110:31-2.
2. Mohs FE. *Chemosurgery: microscopically controlled surgery for skin cancer*. Springfield, IL: Charles C. Thomas, 1978:23.
3. Snow SN, Stiff MA, Bullen R, Mohs FE, Chao WH. Second intention healing of exposed facial-scalp bone after Mohs surgery for skin cancer: review of ninety-one cases. J Am Acad Dermatol 1994; 31:450-4.
4. Wu J, Barisoni D, Menapace L, Ribocco M, Armato U. A novel approach to extend the survival of skin xenografts without entailing general immunosuppression or systemic toxicity. Burns 1993;19: 289-96.
5. Kolenik SA, Leffell DJ. The use of cryopreserved human skin allografts in wound healing following Mohs surgery. Dermatol Surg 1995;21:615-20.
6. Duinslaeger L, Verbeken G, Reper P, Delaey B, Vanhale S, Vander-Kelan A. Lyophilized keratinocyte cell lysates contain multiple mitogenic activities and stimulate closure of meshed skin autograft-covered burn wounds with efficiency similar to that of fresh allogeneic keratinocyte cultures. Plast Reconstr Surg 1996;98:110-7.
7. Eaglstein WH, Iriondo M, Laszlo K. A composite skin substitute (Graftskin) for surgical wounds. a clinical experience. Dermatol Surg 1995;21:839-43.
8. Motta G, Ratto GB, DeBarbieri A et al. Can heterologous collagen enhance the granulation tissue growth? An experimental study. Ital J Surg Sci 1983;13:101-8.
9. Smith KJ, Skelton HG, Barrett TL, Welch M, Beard J. Histologic and immunohistochemical features in biopsy sites in which bovine collagen matrix was used for hemostasis. J Am Acad Dermatol 1996;34:434-8.
10. Leipziger LS, Glushko V, DiBernardo B, et al. Dermal wound repair: role of collagen matrix implants and synthetic polymer dressings. J Am Acad Dermatol 1985;12:409-19.
11. Becker GD, Adams LA, Ikegami K. Collagen-assisted healing of facial wounds after Mohs surgery. Laryngoscope 1994;104:1267-70.
12. Glasgold MJ, Glasgold AI, Silver FH. The use of collagen matrix to enhance closure of facial defects. Ear Nose Throat J 1991;70:531-7.
13. Mian M, Aloisi R, Benetti D, Rosini S, Glasgold AI. Potential role of heterologous collagen in promoting cutaneous wound repair in rats. Int J Tissue React 1992;14:43-52.

daily, we cannot be certain that the three dressing changes needed by patients using the lyophilized bovine collagen matrix were really any different than what would have been found had a control population been instructed to change their dressing only as needed rather than being told to change the dressing daily. Nevertheless, the series has highlighted this quality-of-life issue and demonstrates the problems posed in uncontrolled practice experience.

This report is also important because of the dramatic difference in healing time found for treatment with the lyophilized bovine collagen matrix. The collagen-matrix treated wounds epithelialized an eye-popping three weeks (45%) faster than the conventionally treated historical controls. Can this really be true? The authors are willing to say it is. Admirably, the authors have recorded the time-to-epithelialization in 15 size- and

site-matched wounds, the historic controls, that healed by secondary intention during the time period of the study. We cannot know how many surgeons know the exact number of days it takes for their patients' wounds to heal by secondary intention. Will surgeons who adopt this treatment agree that the healing time it produces is 45% faster than what occurs with their conventional treatments? One might speculate that such a large change would be readily noticeable without concurrent controls. However, it is best to agree with the authors that a

large controlled, multicenter clinical trial is the best way to find out. Otherwise, the relative efficacy of this treatment will remain, as it is with so many others, declared rather than proven, a part of our lifelong uncontrolled experience. Our patients like to believe we really know.

WILLIAM H. EAGLSTEIN, MD
Miami, Florida