ORIGINAL RESEARCH

Efficacy of a Bioresorbable Matrix in Healing Complex Chronic Wounds: An Open-Label Prospective Pilot Study

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ABSTRACT

Objective. The goal of this prospective clinical study was to assess the effectiveness of a novel bioresorbable polymeric matrix impregnated with ionic and metallic silver as a primary wound contact dressing in healing stagnant or deteriorating chronic wounds. **Materials and Methods.** Thirty-two patients with a total of 35 chronic wounds undergoing treatment at the Wound Healing and Hyperbaric Center at Mission Hospital were recruited under a protocol approved by the institutional review board. The wounds included venous stasis ulcers, diabetic foot ulcers, postoperative surgical wounds, burn wounds, and chronic, nonpressure lower extremity ulcers. At baseline, all wounds were nonhealing (ie, stagnant or deteriorating) for a median of 39 weeks (range, 3–137 weeks) and suspected of persistent microbial colonization that had not responded to traditional antimicrobial products and/or antibiotics. The aforementioned matrix was applied to wounds once every 3 days and covered with a secondary dressing. Previously prescribed protocols of care, such as debridement or compression wraps, were continued, but prior antimicrobial dressings or antibiotics were replaced with the matrix. Wound assessments at 3 weeks and 12 weeks post intervention are reported. **Results.** Three patients were excluded due to patients lost to follow-up after initial application. At 3 weeks, 72% of wounds (22/32) had significantly improved healing with an average wound area reduction of 66%. By 12 weeks, 91% of wounds (29/32) either healed completely (ie, fully reepithelialized) or improved significantly with an average wound area reduction of 73%. The matrix was well tolerated; no patient reported discomfort with the application of the matrix. **Conclusions.** The micrometer-thick bioresorbable matrix presents a new form factor to wound management, conforming intimately to the underlying wound bed to exert localized and sustained antimicrobial action of noncytotoxic levels of silver. The application of the matrix on the wound surface in protocols of care was safe and well tolerated, and it facilitated improvements in healing of a majority of the stagnant or deteriorating complex chronic wounds.

KEY WORDS

bioresorbable, antimicrobial, silver, matrix, chronic, wound, infection

INDEX

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The burden of chronic wounds in the United States continues to mount, with annual cost estimates near $25 billion.[1] These chronic wounds are those that are stagnant or deteriorating, increasing in size, exudate, or odor, and generally having clinical signs of infection. They require more frequent clinical visits, costing 2 to 6 times more per week for treatment than acute wounds that are progressing to healing.[2] Standard protocols for the management of such complex wounds are highly variable and often include administering systemic antibiotics to arrest possible evolving wound infection. Effective strategies include wound debridement and cleansing to remove necrotic tissue and reduce bacterial counts. However, debridement is insufficient in removing all bacteria from a wound surface, often resulting in bacterial regrowth from the wound bed interstices. Therefore, a variety of topical antimicrobial formulations and dressings are included as a first-line approach for wound infection management in standard of care protocols with the intent to reduce the use of systemic antibiotics. Such standards of care, however, still suffer from large deficiencies often associated with poor clinical outcomes. The increased prevalence of antibiotic-resistant bacteria stems from the use of systemic antibiotics.[3] Topical antimicrobials require repeated applications due to short residence times in the wound, necessitating frequent and painful dressing changes.[4] Antimicrobial wound dressings with high loadings of antimicrobials, such as silver and iodine,[5,6] have potential to cause high cytotoxicity[7] and have been reported to impair wound healing.[8-13]

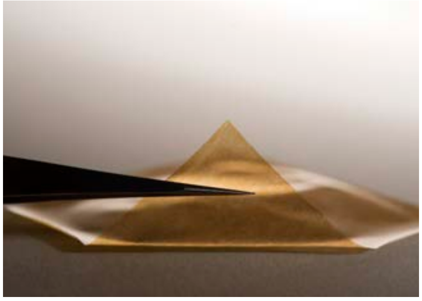

Figure 1. A 5cm x 5cm unit of the matrix held with tweezers on a surface.

The objective of this study was to evaluate the effectiveness of a novel bioresorbable polymeric matrix (**Figure 1**) within protocols used to manage hard-to-heal chronic wounds. The antimicrobial matrix contains ionic and metallic silver within polymeric multilayers in which metallic silver particles provide sustained release of antimicrobial silver ions over several days. The manufacturer recommends using the term *matrix* to describe this bioresorbable porous polymeric multilayer architecture as it provides a scaffold for both uniform loading of silver nanoparticles and a template for cells migration. Other published studies have reported that components of the matrix allow growth and proliferation of fibroblasts[14] and migration of keratinocytes[15] on its surface, as well as supporting normal vascularization and granulation tissue formation in the wound bed.[16] The matrix is reported to be less cytotoxic to mammalian cells,[17] containing only 0.16 mg/in^2 of total silver, which is 50-fold to 100-fold less than that found in traditional silver dressings (eg, ACTICOAT Antibacterial Barrier Dressing [Smith+Nephew, Inc], 6.7 mg/in^2 silver; Silverlon Antimicrobial Dressing [Cura Surgical, an Argentum Medical Company], 35.2 mg/in^2 silver).[18] The ultrathin form factor (thickness, 20 µm) of the matrix facilitates a primary mode of action different than conventional silver dressings. As the matrix absorbs wound fluid, it transforms into a micrometer-thick soft gel that intimately conforms to the contours of an underlying wound bed where bacteria colonize.[17] Most of the silver ions in the matrix are, thus, potentially consumed for antimicrobial action on the wound bed in intimate contact with the matrix.[14] The role of silver in the matrix is not to graft into the tissue, but to prevent colonization in the dressing itself. This mode of action reduces loss of silver ions in wound exudate,[14,17] reducing potential silver cytotoxicity, staining, and irritation[19,20] while potentially enabling increased comfort for patients. The matrix is breathable, allows for the transmission of oxygen and water vapor, and maintains a physiologically moist environment.[17]

Accordingly, the scientific premise of this clinical study was that the micrometer-thick form factor of the matrix with antimicrobial silver could efficiently clear persistent microbial colonization on the surface of chronic wounds stalled in the inflammatory phase and aid in progressing the wound healing process. This study is the first institutional review board (IRB)-approved, open-label, prospective clinical evaluation of the aforementioned matrix in protocols of care for complex, chronic, nonhealing wounds (ClinicalTrials.gov identifier: NCT03204851).

MATERIALS AND METHODS

Matrix intervention

The matrix is cleared by the US Food and Drug Administration (FDA) as a wound dressing indicated for the management of surgical wounds, burn wounds, and chronic ulcers; it is manufactured by Imbed Biosciences, Inc in an FDA-registered International Organization Standard (ISO) 13485 certified facility. The matrix is an electron beam-sterilized, single-use, absorbent ultrathin polymeric matrix (thickness, 20 µm). It is composed primarily of a bioresorbable polymer (polyvinyl alcohol) with a multilayer polymeric surface coating containing ionic and metallic silver (0.16 mg/in^2). When placed on a moist wound surface, the matrix absorbs wound fluid and maintains a moist wound healing environment that aids in the removal of nonviable tissue from the wound (autolytic debridement),[21] the benefits of which could include reduced pain, accelerated neovascularization, and prevention of tissue dehydration.[22] According to its published instructions for use (IFU), biocompatibility of the matrix has been documented through appropriate in vitro and in vivo ISO 10993 standard tests, including cytotoxicity, acute systemic toxicity, subacute/subchronic toxicity, acute intracutaneous reactivity, skin sensitization, and tissue implantation tests. Sustained antimicrobial activity of the matrix has been demonstrated for up to 3 days by relevant standard in vitro microbiological assays in simulated wound fluid. The matrix has been reported to kill more than 4 $\log_{10}$ colony-forming units of microbes most frequently associated with wound infections within 24 hours, including *Staphylococcus aureus* (ATCC 6538), methicillin-resistant *S aureus* (ATCC 33591), vancomycin-resistant enterococci (ATCC 55175), *Pseudomonas aeruginosa* (ATCC 9027), *Escherichia coli* (ATCC 8739), *Klebsiella pneumoniae* (ATCC 4352), *Candida tropicalis* (ATCC 750), and *Candida albicans* (ATCC 10231). The matrix is tested to be nonpyrogenic as well as reported to bioresorb within 7 days.[17]

Study design

This clinical study was conducted in accordance with Title 21 of the Code of Federal Regulations and the Declaration of Helsinki as well as its subsequent amendments and the laws of the United States, where applicable. It was conducted at Mission Hospital's 800-bed southeastern tertiary care center in Asheville, North Carolina, under a protocol reviewed and approved by the Mission Hospital IRB. The patient population included patients referred to the Wound Healing and Hyperbaric Center at Mission Hospital for wound management. This study was designed as a prospective examination of the efficacy and tolerability of the matrix when used in patients with various nonhealing complex chronic wounds that have not responded to protocols of care (including a variety of traditional antimicrobial dressings and ointments and antibiotics). Upon referral to the wound center, the clinical investigator (DH) assessed the patient's medical history, ulcer etiology, and alignment with the study inclusion and exclusion criteria (**Table 1**) to determine potential eligibility for the study. Patients provided written informed consent at the time of initial evaluation and received the matrix at their initial dressing change.

The clinical investigator conducted baseline and follow-up assessments of all patients. The clinical investigator continued the previously prescribed protocol of care for each wound and added the matrix as a primary wound contact dressing to the treatment plan. Any additional antibiotics or primary antimicrobial dressings were discontinued. Briefly, wounds were gently cleaned and irrigated with sterile saline. Surgical or enzymatic debridement protocols were performed, if clinically indicated, to remove excessive necrotic tissue. The matrix was cut to be slightly larger than the size of the wound and applied directly to the moist wound tissue surface. The matrix quickly absorbed moisture and transformed into a soft conforming gel sheet. Multiple sheets of the matrix were tiled if needed to cover the entire wound area. The same secondary dressing used in the patient's ongoing treatment plan was used to cover the matrix. Any specific treatment plan in ongoing protocols of care were continued, including negative pressure wound therapy or compression wraps. No cellular- and/or tissue-based products were used in this study.

The matrix was reapplied once every 3 days, as suggested in the IFU product insert. The matrix was reapplied by the clinical investigator on each patient visit when secondary dressings were changed, depending on the wound healing progression or when clinically indicated (eg, leakage, excessive bleeding, increased pain). The matrix was reapplied at least once weekly in all protocols of care as it is reported to bioresorb within 7 days. No additional antibiotics or topical antimicrobials were administered.

During dressing changes, the secondary dressing was removed, and the wound bed was gently irrigated with sterile saline solution to remove any necrotic tissue. Any residual matrix left in the wound was not removed due to its bioresorbable nature; ultimately, it was cleared from the wound bed by migrating macrophages that break it down and digest it as the wound heals.[16,17]

Study assessments included wound closure (measured as percent of wound area reduction), frequency of dressing changes, pain, clinical evaluation of wound infection, and adverse events (AEs). Wound measurements and photographs were obtained at each clinic visit, as was an in-house patient satisfaction survey. Wounds were photographed at each study session, and the digital photographs were visualized with ImageJ software (National Institutes of Health) by an independent investigator blinded to the treatment to measure total wound area. Data from the study assessments were collected on a separate data collection sheet for each patient. The clinical investigator ensured that data collection sheets were completed properly. All source documents, photo documentation of wounds, and data collection sheets were maintained in individual patient files. Since these wounds were nonhealing at baseline, acceleration in wound healing from the use of the matrix was measured as percent of wound area reduction, according to FDA guidance.[23]

The primary endpoint was the percent of wound area reduction at 3 weeks from baseline. The 3-week time point was chosen based on prior clinical experience of the authors in which significant improvement in wound healing was observed in the nonhealing wounds. Furthermore, such complex wounds require multimodal treatment plans and might not respond to a change in topical antimicrobial dressing alone. Therefore, the clinical investigator recommended that if a wound does not respond to the use of the matrix in protocols of care within 3 weeks, it would be removed from the study. The treatment with the matrix continued for up to 12 weeks, at the discretion of the physician, or until the patient no longer visited the wound care center.

The secondary endpoints were percent of wound area reduction at 12 weeks from baseline, pain, incidence of infection, and patient satisfaction. Patients whose wounds were treated with the matrix but did not heal completely within 12 weeks continued to be seen by the clinical investigator.

The AEs were documented and reported in accordance with FDA rules and regulations. The time of onset (if known), duration, intensity, relationship to the test product, treatment, and follow-up were recorded. The clinical investigator assessed causality between the AE and the administration of the matrix. An AE was considered *not related* if the event was most likely produced by other factors, such as the patient's clinical condition, intercurrent illness, or concomitant medications or procedures. In addition, an AE was considered *not related* if the event did not follow a known response pattern to the matrix or the temporal relationship of the event to the administration of the matrix made a causal relationship unlikely; a lack of an alternative explanation for the AE was also considered. An AE was considered *related* if a reasonable temporal sequence of the event with the administration of the matrix existed. Also, on the basis of the known pharmacological action of the matrix, an AE was considered *related* if the known or previously reported AE to the matrix seemed likely, or if there was a lack of alternative explanation for the AE.

Table 1. Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Existing patient	Age <18 y
Age ≥18 y	Pregnant or nursing
Able to provide consent for self	
Nonhealing or stalled chronic venous stasis ulcer, DFU, pressure ulcer (NPIAP), or other complex wounds	

y: year; DFU: diabetic foot ulcer; NPIAP: National Pressure Injury Advisory Panel

Table 2. Wound types treated and nonhealing wound duration prior to treatment with the matrix

WOUND TYPE	NO. OF WOUNDS	MEDIAN AGE OF PATIENTS; y (RANGE)	NONHEALING WOUND DURATION PRE-STUDY INCLUSION		
			<3 mos	3–6 mos	>6 mos
Venous stasis	19	66 (43–95)	6	3	10
DFU	8	62 (46–72)	0	0	8
Postop	3	56 (25–61)	1	0	2
Trauma	2	69 (51–86)	1	0	1
Pressure ulcer (NPIAP)	1	62	1	-	-
Pilonidal cyst	1	22	1	-	-
Burn	1	43	1	-	-
Total	**35**	**62 (22–95)**	**11**	**3**	**21**

y: year; mos: month; DFU: diabetic foot ulcer; NPIAP: National Pressure Injury Advisory Panel

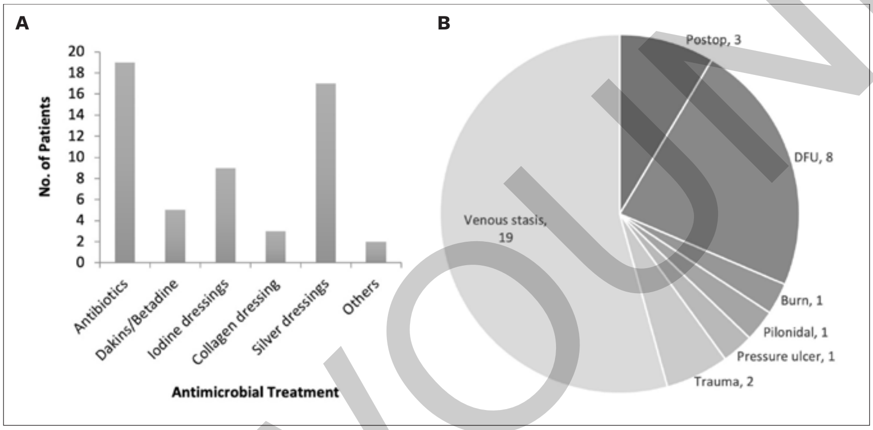

Figure 2. (A) Various antimicrobial treatments administered to the patients prior to starting the treatment plan with the matrix; and (B) the number of different types of wounds included in the study (N=35).

RESULTS

Baseline characteristics

A total of 32 patients who underwent treatment at the wound care center met the inclusion criteria listed in **Table 1** and provided written consent to participate in the clinical study. One patient had 3 diabetic foot ulcers (DFUs), and another patient had 2 venous stasis ulcers; thus, a total of 35 wounds were included in the study. At baseline, all wounds were nonhealing (ie, stagnant or deteriorating) and showed signs of clinical infection (ie, pain, erythema, edema, warmth, malodor, purulent exudate, discoloration of granulation tissue, or friable granulation tissue).[24,25] Patients who did not respond to prior protocols of care, including systemic antibiotics or topical antimicrobial agents, were suspected to have persistent microbial colonization. The patients' age, wound types, and duration for which their wounds were nonhealing prior to inclusion in the study are shown in **Table 2**. The median age of patients enrolled in the study was 62 years (range, 22–95 years). Prior to the study, all 35 wounds had been nonhealing for a median of 39 weeks (range, 3–137 weeks). Venous stasis ulcers and DFUs had been nonhealing the longest with a median of 37 and 52 weeks, respectively. The average wound surface area at the beginning of the study was 6.7 cm^2 (range, 0.1 cm^2–33 cm^2); the median wound surface area was 2.1 cm^2. All patients had undergone multiple wound care treatment plans with various antibiotics and topical antimicrobials, including wound dressings containing iodine, betadine, and silver (**Figure 2**). Among 35 chronic wounds included in the study, venous stasis ulcers comprised the majority (54%) of wounds (19/35) followed by DFUs (23%; 8/35) (**Figure 2**).

Outcomes: primary endpoint (3-week assessment)

Three venous stasis ulcers were excluded from the analysis due to incomplete data sets and no follow-up visit after the first application of the matrix. After 3 weeks of treatment with the matrix, 72% (22/32) of the wounds included in the analysis had an average wound area reduction of 66% from baseline. Of the 16 venous stasis ulcers, 11 improved by an average closure rate of 60%, and 6 of 8 DFUs improved by an average wound area reduction of 79% (**Table 3**). At the 3-week assessment, the burn wound and postoperative wounds had average wound area reduction of 38% and 58%, respectively.

Outcomes: secondary endpoint (12-week assessment)

After the primary 3-week assessment, patients continued to receive wound treatment with the matrix at least once weekly for up to 12 weeks until complete wound closure or until patients were lost to follow-up. A total of 26 wounds were treated with the matrix beyond the 3-week period. Over 12 weeks, 91% of the wounds (29/32) included in the analysis either healed completely (ie, fully reepithelialized) or documented significant improvement in healing with an average wound area reduction of 73% (**Figure 3**). Venous stasis ulcers and DFUs achieved an average wound area reduction greater than 75%, with visual signs of healthy granulation tissue formation and reepithelialization. There were 12 wounds with greater than a 90% wound area reduction. The burn wound was completely closed

Table 3. Clinical status for each wound type after 3 weeks of treatment with the matrix

WOUND TYPE	NONHEALING PRE-STUDY; WK (MEDIAN)	PRIMARY ENDPOINT: % WOUND AREA REDUCTION AT THE END OF 3 WK
Venous stasis	37	11/16 wounds improved with an average % area reduction of 60% (Note: 3 patients were excluded from analysis due to no follow-up after the first application of the matrix)
DFU	52	6/8 wounds improved with an average % area reduction of 79%
Postop	37	2/3 wounds improved with an average % area reduction of 58%
Trauma	27	1/2 wounds improved with an average % area reduction of 85%
Pressure ulcer (NPIAP)	6	Improved with an average % area reduction of 45%
Pilonidal cyst	4.5	Improved with an average % area reduction of 94%
Burn	5	Improved with an average % area reduction of 38%
Summary	**39**	**22/32 wounds (ie, 72% of the total wounds included in the analysis) Improved with an average % area reduction of 66%**

wk: week; DFU: diabetic foot ulcer; NPIAP: National Pressure Injury Advisory Panel

in 9.5 weeks. The 3 venous stasis ulcers, each of which was exudating, continued to increase in size and were removed from the evaluation after 4 weeks of weekly treatment with the matrix.

Patient experience

From a qualitative perspective, the application of the matrix in protocols of care for chronic wounds was well tolerated by the patients in the study. No patient reported discomfort from the application of the matrix and associated dressing changes. There were no matrix-related AEs reported during the duration of this study.

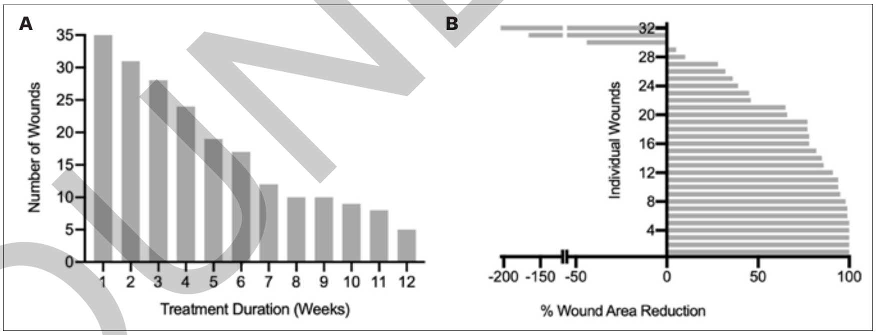

Figure 3. (A) Duration of the treatment with the matrix for a given number of wounds; and (B) percent of wound area reduction achieved for each of the 32 wounds included in the study analysis during 12 weeks of treatment with the matrix.

Representative cases

Case 1: venous stasis ulcer. A 58-year-old female presented with a nonhealing venous stasis ulcer. The wound had been stalled for 52 weeks at baseline. In prior treatment plans, the patient had received antibiotics, and the wound had been treated with bacitracin, Dakin's solution, or hydrogen peroxide in conjunction with compression therapy but showed no improvement. The wound then was treated weekly with the matrix and compression therapy. The initial size of the wound at the start of treatment with the matrix was 4.6 cm^2. After 3 weeks of treatment with the matrix, the wound reduced in size to 2.3 cm^2 (% wound area reduction = 51%). Additional weekly treatments with the matrix resulted in steady closure, with complete closure by the 12-week evaluation (**Figure 4**). In this case, the matrix paired with compression therapy was associated with a positive outcome.

Case 2: venous stasis ulcer. A 72-year-old male presented with a nonhealing venous stasis ulcer. The wound had been stalled for 8 weeks at baseline. In prior treatment plans, the patient had received antibiotics, and the wound had been treated with an iodine-based antimicrobial absorbent pad or a silver foam in conjunction with compression therapy but showed no improvement. The wound then was treated with the matrix at weekly evaluation and compression therapy. The initial size of the wound at the start of treatment with the matrix was 5.3 cm^2. After 3 weeks of treatment with the matrix, the wound reduced in size to 2.7 cm^2 (% wound area reduction = 49%). Additional weekly treatments with the matrix paired with compression therapy resulted in steady closure to 0.1 cm^2 (% wound area reduction = 99%) documented by the 10-week evaluation (**Figure 5**).

Case 3: DFU. A 68-year-old male presented with a nonhealing DFU. The wound had been stalled for 31 weeks at baseline. In prior treatment plans, the patient had received gentamycin and treated with topical antimicrobials along

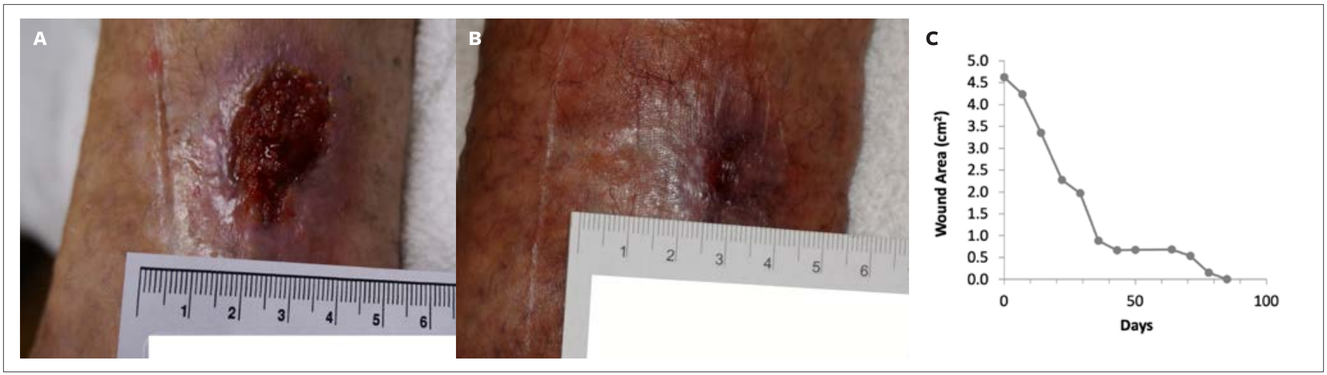

Figure 4. Case 1: a 58-year-old female presented with a nonhealing venous stasis ulcer stalled for 52 weeks. (A) Ulcer at the baseline; (B) ulcer was completely closed after 12 weeks (85 days) of once-weekly application of the matrix in conjunction with compression therapy; and (C) progression of wound closure with time—each data point represents a clinic visit when the matrix was reapplied.

Figure 5. Case 2: a 72-year-old male presented with a nonhealing venous stasis ulcer stalled for 8 weeks. (A) Ulcer at baseline; (B) ulcer was completely closed after 8 weeks (72 days) of once-weekly application of the matrix in conjunction with compression therapy; and (C) progression of wound closure with time—each data point represents a clinic visit when the matrix was reapplied.

Figure 6. Case 3: a 68-year-old male with a nonhealing diabetic foot ulcer stalled for 31 weeks. (A) Ulcer at baseline; (B) ulcer was 77% closed after 4 weeks (26 days) of 2 to 3 weekly applications of the matrix; and (C) progression of wound closure with time—each data point represents a clinic visit when the matrix was reapplied.

with surgical debridement but showed no improvement. The wound then was treated with the matrix 2 to 3 times per week. The initial size of the wound was 10.6 cm^2. After 4 weeks, the wound had reduced in size to 2.4 cm^2 (% wound area reduction = 77%) (**Figure 6**). The patient did not return for subsequent follow-up.

Case 4: burn wound. A 43-year-old female presented with a nonhealing full-thickness burn wound; the patient had no comorbidities. The wound had been stalled for 5 weeks at baseline and suspected of infection. In prior treatment plans, the patient had received antibiotics, and the wound had been treated with silver sulfadiazine cream, an iodine-based absorbent pad, and a silver-based foam dressing but showed no improvement. The wound then was treated with weekly applications of the matrix and covered

Figure 7. Case 4: a 43-year-old female with a full-thickness burn wound stalled for 5 weeks. (A) Burn wound at baseline; (B) wound was completely closed after 12 weeks (85 days) of once-weekly application of the matrix; and (C) progression of wound closure with time—each data point represents a clinic visit when the matrix was reapplied.

Figure 8. Case 5: a 22-year-old female with a postop pilonidal cyst stalled for 4 weeks. (A) Wound at baseline; (B) wound was 98% closed after 6 weeks (43 days) of 2 to 3 weekly applications of the matrix; and (C) progression of wound closure with time—each data point represents a clinic visit when the matrix was reapplied.

with gauze dressings. The wound did not require debridement during weekly evaluations, and no oral or topical antibiotics were administered. The initial size of the wound at the start of treatment with the matrix was 24.1 cm^2. Three weeks after weekly treatment with the matrix, the wound reduced in size to 15 cm^2 (% wound area reduction = 38%). Additional weekly treatments with the matrix resulted in steady closure of the previously stalled wound. Complete closure was achieved by the 12-week evaluation (**Figure 7**).

Case 5: postoperative pilonidal cyst. A 22-year-old female presented with a nonhealing postoperative pilonidal cyst surgical site infection. The wound had been stalled for 4 weeks at baseline. In prior treatment plans, the wound had been treated with Dakin's solution, followed by negative pressure wound therapy but showed no improvement. The wound then was treated with the matrix 2 to 3 times per week along with concurrent application of negative pressure wound therapy. The initial size of the wound was 33.3 cm^2. After 6 weeks of regular treatment with the matrix, the wound had reduced in size to 0.6 cm^2 (% wound area reduction = 98%) (**Figure 8**).

DISCUSSION

Chronic wounds with persistent microbial colonization on the tissue surface can remain stalled in the inflammatory phase of healing for months and may never progress without significant intervention.[26] Moreover, the longer a chronic wound remains open means the risk of acquiring a multispecies infection increases.[27] Wound care protocols involving combination approaches of debridement and broad-spectrum antimicrobials are increasingly adopted in the management of chronic wounds. Topical antimicrobial formulations play a key role in arresting microbial colonization on the surface of wound tissue as they can reduce the need for systemic antibiotics.[1] However, traditional antimicrobial dressings are designed as large reservoirs that can replenish the loss of cationic antimicrobials (eg, silver, iodine) that were deactivated immediately in protein-rich wound exudate.[14] Thus, the high concentrations of cationic antimicrobials build up in wound tissue and cause high cytotoxicity[7]; also, these antimicrobials are reported to be associated with impairment of wound healing.[8-13]

The novel bioresorbable polymeric matrix evaluated in this study has been designed specifically to address this limitation of traditional antimicrobial dressings. Conventional silver dressings generate high cytotoxic concentrations of silver in wound fluid to achieve antimicrobial action at the wound bed where bacteria colonize.[14] In contrast, conformal contact of the micrometer-thick matrix with wound bed, owing to its large surface area to cross-sectional area ratio, provides intimate contact of silver ions with the microbes on the wound bed.[14,17] This exerts effective antimicrobial therapy while using 50 times to 100 times less silver content than traditional silver dressings. Most of the silver ions in the matrix are potentially consumed for antimicrobial action on the wound bed,[14,17] thus reducing their loss in wound exudate and potential cytotoxicity, staining, and irritation from dressings.[19,20] The matrix is made of nanometer-thick polymeric multilayers impregnated with metallic silver particles, which dissolve over time in wound fluid to release silver ions.[14,17] This allows the matrix to provide sustained antimicrobial activity for up to 3 days in simulated wound fluid in vitro, as listed in the matrix's IFU.

This is the first IRB-approved human clinical study on this bioresorbable matrix that is designed to evaluate its effectiveness in protocols for management of hard-to-heal wounds that were unresponsive for months to traditional antimicrobial dressings and antibiotics. The matrix was employed as a primary wound contact matrix, which replaced the other primary antimicrobial dressing or antibiotics used in the prior treatment plans. Since all of the wounds at baseline were stalled (ie, either stagnant or deteriorating), prior treatment plans with traditional antimicrobial dressings and antibiotics had little impact on wound healing. This is likely indicative of persistent microbial colonization that was tolerant of such traditional antimicrobial dressings and care.

Results of the study show that inclusion of the matrix in the treatment plan helped jump start the healing process of these stalled wounds. Within 3 weeks, 72% of wounds demonstrated significantly improved healing; within 12 weeks, 91% of wounds either healed completely (fully reepithelialized) or significantly improved. The outcome was consistent across various wound etiologies and chronic wound types. The only difference between new and prior treatment plans was the replacement of traditional antimicrobial dressings with the matrix as the primary wound dressing. These outcomes support the scientific premise that the micrometer-thick form factor of the matrix with metallic silver particles enabled antimicrobial silver ions to work more effectively in clearing persistent microbial colonization hidden in crevices of a tissue surface, where traditional antimicrobial dressings used in prior treatment plans were less effective.

An additional key benefit of the matrix is that it is primarily made of bioresorbable polymers,[17] which circumvents the need for its painful removal and facilitates its potential prolonged use in multimodal treatment plans involving compression wraps or negative pressure. This easy and versatile application of the matrix allowed a single clinical investigator in this study to include the matrix as the primary dressing in all wound care plans without changing the remainder of the care plan. Sustained antimicrobial activity of the matrix limited dressing changes to once every 3 days. Secondary outcomes in the study sought to incorporate patient experience into the evaluation of the matrix. Because many patients with chronic wounds have additional comorbidities and a high level of contact with the medical system, the secondary goal was to create an effective, well-tolerated wound care approach that could minimize visits to the clinic for dressing changes. None of the patients in this study reported pain with any application of the matrix or associated dressing changes. These features of the matrix can potentially improve the quality of life for patients with chronic wounds and increase the likelihood that this population may be compliant with their treatment course.

The 3 venous stasis ulcers that enlarged over the first 4 weeks of evaluation with the matrix were highly exuding and had previously been managed unsuccessfully with multiple antimicrobials and antibiotics, including silver dressings and an antimicrobial absorbent pad, under compression. These longstanding wounds ranged in duration from 5 to 21 months. It may be possible that their exuding nature did not respond to the ultrathin polymeric matrix dressing. These ulcers emphasize that chronic wounds might not respond to a change in topical antimicrobial dressing alone because they involve complex comorbidities and systemic diseases that require multimodal treatment plans.

The study outcomes conclude that application of the matrix directly to the wound surface was safe, well tolerated, and facilitated improvements in healing of most of the stagnant or deteriorating complex chronic wounds. The clinical investigators would recommend considering the matrix for the management of complex wounds in conjunction with standard protocols of care, such as debridement in DFUs and compression therapy in venous stasis ulcers. The matrix should be applied to clinically clean ulcers. Wounds should be clinically inspected at each dressing change and appropriately debrided weekly if there are clinical signs of bioburden or slough.

LIMITATIONS

A limitation of this clinical study is the small sample size (N = 35 wounds; 32 patients). While the majority of the wounds included venous stasis ulcers (n = 19) and DFUs (n = 8), the additional 4 wound types had 1 to 3 patients in the subset groups. This limits generalizability about wound healing efficacy of the matrix in these subgroups and would be a natural area for future clinical studies. Another limitation of the study is that the same clinical investigator did all evaluations during the study. Although he is an experienced wound care physician, wound measurement and evaluation includes a subjective component and introduces the possibility of bias in evaluating wound characteristics and in measurement. In future studies, using additional evaluators would improve interrater reliability. Based on the promising outcomes with the matrix in a variety of chronic wounds in this first prospective clinical study, the authors recommend further evaluation of this novel matrix in future randomized controlled trials in preselected wound types, such as a cohort of only diabetic foot ulcers or burns or surgical wounds.

CONCLUSIONS

This clinical study evaluated the effectiveness of a novel bioresorbable matrix as an intervention to stalled chronic wounds that were stagnant or deteriorating for a median of 39 weeks. The wounds were not responding to prior treatment plans with antibiotics and traditional antimicrobial dressings, and were suspected of persistent microbial colonization prior to study inclusion. When the matrix was included in the treatment plan, 72% of the wounds had shown improved healing within 3 weeks, while 91% of the wounds either healed completely (ie, fully reepithelialized) or improved significantly within 12 weeks, with an average wound area reduction of 73%. Patients tolerated the matrix with no reports of discomfort, pain, or AEs. The study outcomes concluded that the application of the matrix directly to the wound surface was safe and well tolerated as well as facilitated improvements in healing of the majority of the stagnant or deteriorating complex, chronic wounds. The micrometer-thick form factor of the matrix with ionic and metallic silver appeared to be an effective alternative to traditional antimicrobial dressings in the management of complex, nonhealing wounds. The results emphasize that this bioresorbable matrix technology may play a significant role in the effective management of hard-to-heal wounds that are unresponsive to standard of care and could be an effective primary antimicrobial wound dressing in protocols of care for complex wounds at risk of infection.

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REFERENCES

1. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. *Adv Ther*. 2017;34(3):599–610. doi:10.1007/s12325-017-0478-y
2. Harding K, Posnett J, Vowden K. A new methodology for costing wound care. *Int Wound J*. 2013;10(6):623–629. doi: 10.1111/iwj.12006
3. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control*. 1995;23(2):87–94. doi:10.1016/0196-6553(95)90104-3
4. Sheridan R, Petras L, Lydon M, Salvo P. Once-daily wound cleansing and dressing change: efficacy and cost. *J Burn Care Rehabil*. 1997;18(2):139–140. doi:10.1097/00004630-199703000-00008
5. Ip M, Lui SL, Poon VKM, Lung I, Burd A. Antimicrobial activities of silver dressings: an in vitro comparison. *J Med Microbiol*. 2006;55(Pt 1):59–63. doi: 10.1099/jmm.0.46124-0
6. Mooney EK, Lippitt C, Friedman J. Silver dressings. *Plast Reconstr Surg*. 2006;117(2):666–669. doi:10.1097/01.prs.0000200786.14017.3a
7. Okan D, Woo K, Sibbald RG. So what if you are blue? Oral colloidal silver and argyria are out: safe dressings are in. *Adv Skin Wound Care*. 2007;20(6):326–330. doi:10.1097/01.ASW.0000276415.91750
8. Hidalgo E, Bartolomé R, Barroso C, Moreno A, Domínguez C. Silver nitrate: antimicrobial activity related to cytotoxicity in cultured human fibroblasts. *Skin Pharmacol Appl Skin Physiol*. 1998;11(3):140–151. doi:10.1159/000029820
9. Kristiansen S, Ifversen P, Danscher G. Ultrastructural localization and chemical binding of silver ions in human organotypic skin cultures. *Histochem Cell Biol*. 2008;130(1):177–184. doi:10.1007/s00418-008-0415-x
10. Van Den Plas D, De Smet K, Lens D, Sollie P. Differential cell death programmes induced by silver dressings in vitro. *Eur J Dermatol*. 2008;18(4):416–421. doi:10.1684/ejd.2008.0437
11. Trop M, Novak M, Rodl S, Hellbom B, Kroell W, Goessler W. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. *J Trauma*. 2006;60(3):648–652. doi:10.1097/01.ta.0000208126.22089.b6
12. Burd A, Kwok CH, Hung SC, et al. A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant, and animal models. *Wound Repair Regen*. 2007;15(1):94–104. doi:10.1111/j.1524-475X.2006.00190.x
13. Wang X-Q, Chang H-E, Francis R, et al. Silver deposits in cutaneous burn scar tissue is a common phenomenon following application of a silver dressing. *J Cutan Pathol*. 2009;36(7):788–792. doi:10.1111/j.1600-0560.2008.01141.x
14. Agarwal A, Weis TL, Schurr MJ, et al. Surfaces modified with nanometer-thick silver-impregnated polymeric films that kill bacteria but support growth of mammalian cells. *Biomaterials*. 2010;31(4):680–690. doi:10.1016/j.biomaterials.2009.09.092
15. Gorouhi F, Shah NM, Krishna Raghunathan V, et al. Epidermal growth factor functionalized polymeric multilayer films: interplay between spatial location and bioavailability of EGF. *J Invest Dermatol*. 2014;134(6):1757–1760. doi:10.1038/jid.2014.7
16. Guthrie KM, Agarwal A, Teixeira LBC, et al. Integration of silver nanoparticle-impregnated polyelectrolyte multilayers into murine splinted cutaneous wound beds. *J Burn Care Res*. 2013;34(6):e359–e367. doi:10.1097/BCR.0b013e31827e7ef9
17. Herron M, Agarwal A, Kierski PR, et al. Reduction in wound bioburden using a silver-loaded dissolvable microfilm construct. *Adv Healthc Mater*. 2014;3(6):916–928. doi:10.1002/adhm.201300537
18. Rajendran S, ed. The Textile Institute Book Series. In: *Advanced Textiles for Wound Care*. 2nd ed. Woodhead Publishing; 2018.
19. Rustogi R, Mill J, Fraser JF, Kimble RM. The use of Acticoat in neonatal burns. *Burns*. 2005;31(7):878–882. doi:10.1016/j.burns.2005.04.030
20. Zweiker D, Horn S, Hoell A, Seitz S, Walter D, Trop M. Semi-permanent skin staining associated with silver-coated wound dressing Acticoat. *Ann Burns Fire Disasters*. 2014;27(4):197–200.
21. Agarwal A, McAnulty JF, Schurr MJ, Murphy

CJ, Abbott NL. Polymeric materials for chronic wound and burn dressings. In: Farrar D, ed. *Advanced Wound Repair Therapies.* ScienceDirect; 2011:186–208.
22. Field FK, Kerstein MD. Overview of wound healing in a moist environment. *Am J Surg*. 1994;167(1A):2S–6S. doi: 10.1016/0002-9610(94)90002-7
23. US Department of Health and Human Services. Guidance for industry: chronic cutaneous ulcer and burn wounds—developing products for treatment. June 2006.
24. Cutting KF, Harding KG. Criteria for identifying wound infection. *J Wound Care*. 1994;3(4):198–201. doi:10.12968/jowc.1994.3.4.198
25. Gardner SE, Frantz AR, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. *Wound Repair Regen*. 2001;9(3):178–186. doi:10.1046/j.1524-475x.2001.00178.x
26. Iqbal A, Jan A, Wajid MA, Tariq S. Management of chronic non-healing wounds by hirudotherapy. *World J Plast Surg*. 2017;6(1):9–17.
27. Siddiqui AR, Bernstein JM. Chronic wound infection: facts and controversies. *Clin Dermatol*. 2010;28(5):519–526. doi:10.1016/j.clindermatol.2010.03.009