

Restarting the Healing Process of Chronic Wounds Using a Novel Desiccant: A Prospective Case Series

[Carlo Alberto Bignozzi](#)

[Bert J. Quint](#)

[Alberto Cogo](#)

Keywords

[Chronic Wound](#)

[Desiccant](#)

[Debridement](#)

[Biofilm](#)

[Inflammation](#)

[Volume 33 - Issue 1 - January 2021](#)

ISSN 1044-7946

Index Wounds 2020;33(1):1–8. doi:10.25270/wnds/2021.0108

Abstract

Introduction. Chronic skin wounds represent a major global health problem and financial burden. The blocked healing process of chronic wounds involves excess inflammatory proteins, persistent microbial burden, and often, drug-resistant biofilm on the wound bed. Wound-bed debridement is considered crucial to restart the healing process.

Objective. The authors developed a novel desiccant (desiccating agent A) to serve as a new form of chemical debridement. The objective is to establish the working mechanism of desiccating agent A. **Materials and Methods.**

Desiccating agent A was exposed to 7 pathogens in vitro and a prospective trial investigation was performed in vivo on 10 cases to establish a timeline to reach granulation. **Results.** The growth of a pool of the 7 pathogens showed an inhibition ring at 24 hours was 54 mm ± 5 mm. The prospective trial investigating 10 cases (5 females, 5 males) had a median age of 72.5 years (range, 50–90 years). The duration of the ulcers ranged from 6 weeks to 52 weeks (interquartile range, 6–24 weeks). The wound bed (median area, 64 cm²) was rinsed and dried. Desiccating agent A was applied directly to the wound bed with a gloved finger; after 30 to 60 seconds, desiccating agent A was rinsed and the remaining desiccated material was mechanically removed with dry sterile gauze. The wound bed was dried and covered with sterile gauze soaked in fitostimoline; dressings were changed as needed. The only observed side effect, transient pain, graded on a visual analog scale. Pain intensity ranged from 1 to 7 on a scale from 0 to 10. No nodules, welts, or blisters were observed. Median time to full granulation was 20.5 days (range, 7–78 days). **Conclusions.**

These data support continued development of desiccating agent A as a chemical debridement agent.

Introduction

Chronic skin wounds represent a major global health problem and financial burden.^{1,2} Their prevalence among the general population is approximately 1.5% and is higher among the elderly.² Because risk factors include increased age and comorbidities such as diabetes, which is occurring in increasingly younger populations, the incidence of chronic skin wounds is expected to rise in the next decade.^{2,3} In particular populations, such as patients with diabetes, the prevalence of chronic ulcers ranges from 1.5% in Australia to 13% in North America and 16.6% in Belgium.^{2,4}

Wounds that have failed to heal or reduce in size by 4 weeks to 12 weeks are considered to be chronic wounds.^{3,5} The healing of chronic wounds is dependent on their size as well as the patient's health status, concurrent medications, and treatments.⁶ The healing process of chronic wounds usually ranges from 6 weeks to more than 1 year, including wounds treated at specialized wound care clinics. Chronic wounds with different etiologies (venous insufficiency, peripheral arterial disease, diabetic neuropathy, pressure ulcers, and vasculitis) share several mechanisms that can halt the healing process: the presence of excessive inflammatory cells and proteins (cytokines and proteases),⁷ persistent low-grade microbial burden, and often drug-resistant biofilm.⁶ Excessive and prolonged presence of inflammatory mediators, proinflammatory

macrophages, and neutrophils in the wound bed contribute to the development and persistence of chronic wounds.⁷ These mechanisms can inhibit progression through the 3 steps of wound healing: removal of necrotic and nonvital material (autolytic debridement) by inflammation (eg, macrophages), neovascular growth, and proliferation of dermal/epidermal cells.

Biofilms consist of an extracellular polymeric matrix that shelters aggregates of bacteria and/or fungi so they are extremely tolerant to antimicrobial treatment and the host defense.^{8,9} Chronic wounds vary in the extent of microbial burden and presence of biofilm, which has been observed microscopically in the chronic wounds of 60% to 100% of patients.^{9,10} Chronic wound microbiota (top 30 species) from approximately 80% of patients (35/43) induced slough and exudate in a murine chronic wound model, indicating that microbiota from chronic wounds can play a major role in halting the healing process.¹¹ Interestingly, chronic diabetic foot ulcers examined with molecular diagnosis of biofilm followed with biofilm-based wound treatment management showed faster healing, displayed a higher response rate, and cost less per patient by 68% in a retrospective comparison to those treated with standard of care.¹²

Current chronic wound management often involves surgical debridement to remove nonvital and potentially infectious materials and is combined with appropriate dressings¹³ that support the TIME framework (tissue, infection/inflammation, moisture balance, and edge of wound) for the individual situation.⁹ Types of debridement include surgical, chemical, enzymatic, biologic (maggots), and autolytic. Although only sharp and surgical debridement effectively remove most slough, biofilm, and nonvital tissue in a single-step procedure,⁹ surgical debridement requires special teams and access to operating rooms, which are associated with high costs. Sharp debridement can be performed in some physician offices or at the bedside, depending on the facility. Reinfection is a major concern, and patient compliance can decrease with need for multiple sessions. Other types of debridement that are currently available require several weeks to be effective. Because wound management is predominately performed by nurses in the real world,¹⁴ the authors searched for an easily administered, nonsurgical, effective wound bed debridement treatment that would in many cases restart the wound healing process.

Because research has shown that biofilm can be removed from teeth by an aqueous phenolsulfonic/sulfuric acid solution with desiccating properties,^{15,16} the authors postulated that a topical desiccating agent could be beneficial in terms of antibacterial effect, biofilm destruction, and inflammatory protein denaturation and removal. As support for use in chronic wounds, Wolcott has described 3 recalcitrant wound cases in which the healing process had restarted and was continued with weekly surgical debridement followed by local treatment with an aqueous phenolsulfonic/sulfuric acid solution with desiccating properties.¹⁷ To reduce the caustic nature of the desiccant, the authors developed a novel hygroscopic gel (henceforth desiccating agent A) that contains 99% methane sulfonic acid, dry proton acceptors, and dimethyl sulfoxide, which acts as a biofilm penetration enhancer. Herein, the authors describe the in vitro antimicrobial activity of desiccating agent A against a pool of several bacteria common in biofilms on lower extremity wounds¹⁸ and chronic osteomyelitis of the jaw.¹⁹ This study also shows the agent's desiccating effect on the wound bed, its effect on progression to granulation, and its side-effect profile from an initial open-label prospective case trial with patients with chronic wounds in the lower extremity. A protocol for application of desiccating agent A is presented in detail.

Materials and Methods

Desiccating agent A (Debrichem, DEBx Medical) is a novel dehydrating agent with strong desiccating properties when applied to organic material. It is formulated by mixing 99% methane sulfonic acid with proton acceptors and dimethyl sulfoxide, as described in patent application PTC NR: IB2019/051146. The product is stable for 24 months in the temperature range from -20°C to +55°C.

Antimicrobial activity

Cultures of *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 10536), *Pseudomonas aeruginosa* (ATCC 15442), *Enterococcus hirae* (ATCC 10541), and *Candida albicans* (ATCC 1023) were purchased from Diagnostic International distribution S.p.A. Cultures of *Tannerella forsythia* and *Porphyromonas gingivalis* were obtained from Eurofins Genomics MWG Operon.

Tryptone soy agar (TSA) petri plates (100 mm) were inoculated with 100 µL of the microbial pool (1.5×10^{12} – 5×10^{12} colony-forming units [CFU]/mL) consisting of *S aureus*, *E coli*, *P aeruginosa*, *E hirae*, *C albicans*, *T forsythia*, and *P gingivalis*. A 50 µL desiccating agent A sample was placed in the center of the plate; plates were incubated at 37°C for 24 hours. The size of the inhibition rings were evaluated. Experiments were performed in replicates of 2 and were repeated twice.

Patient ethics

This study was approved by the local ethical committee. The aim of the study was explained to all patients, and they provided written informed consent before enrollment.

Patient selection

Patients seeking wound care at Villa Berica Hospital between September 2018 and December 2018 were considered for enrollment in this series if their leg had a chronic wound of at least 6 weeks' duration. After reviewing prior medical history, which included prior wound treatments at the previous ambulatory center, patients were screened for the presence of a pedial artery pulse in the foot with the ulcer to exclude those with clinically relevant peripheral arterial disease. In the authors' facility, sharp debridement is performed solely as surgical debridement in the operating room with a surgeon and anesthesia assistant. No patients had received surgical debridement in the operating room nor debridement with a scalpel for the study ulcer. The length and width of the wound bed were measured, and the inclusion criteria did not set a minimum or maximum size of the wound bed. Patients were excluded if they had nonrevascularized critical limb ischemia, fever or sepsis indicating candidacy for systemic antibiotic treatment, a purulent abscess needing surgical evacuation, or a cancer-related ulcer.

Treatment methodology

Patients were positioned on an ambulatory bed in a comfortable position. All bandages, wound dressings, and remaining previous medications were removed by saline rinsing. The wound bed was cleaned with dry gauze with sufficient friction to remove the already detached necrotic material and slough. The wound bed was completely dried.

Desiccating agent A gel was applied to the wound bed ($\sim 1 \text{ mL}/100 \text{ cm}^2$) and was evenly distributed with a gloved finger within 30 to 60 seconds, with covering of larger wound beds and margin requiring up to a total of 60 seconds. Approximately 1 cm margin of surrounding healthy skin was also treated to remove the biofilm and reduce the risk of new contamination of the wound bed by migrating pathogens. After desiccating agent A had remained on the wound bed for a minimum of 30 seconds (maximum 60 seconds, including time during the covering of the wound bed), the wound bed and margin were rinsed with saline. The wound bed was rubbed with dry sterile gauze to remove the detachable material. The wound bed was dried with a sterile gauze and covered with a sterile gauze soaked in the aqueous extract of *Triticum vulgare* (Fitostimoline garze impregnate; Famaceutici S.p.A.).²⁰ (The fitostimoline-treated gauze is referred to as *soaked gauze* hereafter). No other medication was allowed. A wound diaper was applied over the sterile soaked gauze as secondary treatment if excessive exudation was expected. A light bandage, or a compression stocking, was applied when indicated. The development of immediate or late side effects was carefully investigated.

Follow-up

All patients were invited to return to the center at 1-week intervals, or earlier in the case of excessive exudation, untreatable pain, or fever. At these visits, bandages were removed and the wounds were rinsed, cleaned with dry sterile gauze, inspected, and covered with new sterile soaked gauze. Desiccating agent A was reapplied only in the case that the operator, after rinsing the wound bed, considered it a necessary treatment due to the presence of necrotic material, slough, and/or infected tissues. The rationale and dates for subsequent desiccating agent A application(s) in the individual patients were recorded.

Endpoints

The visit at which the wound had progressed to 100% granulation was noted. After the 6-week period, the patients were categorized by wound status. Substantial improvement was defined as the presence of good granulation tissue formation, epidermal tissue growing from wound edges, and the absence of nonvital debris and infection. The patients in the substantially improved group were treated as preferred by the attending clinician (ie, spontaneous reepithelialization or skin graft). Alternatively, if the wound status did not show improvement or showed deterioration, the patients in the unimproved group were considered nonresponsive to desiccating agent A and became candidates for another form of wound debridement.

Side effects and adverse events

Patients reported pain duration and pain intensity by using a well-established, patient-reported visual assessment scale of 100 mm in length. These patient-reported outcomes were compiled only from patients without sensory neuropathy (ie, they retained sensitivity to pain in their feet). During administration and follow-up, any other side effects observed by the operator or reported by the patients were recorded.

Results

Antimicrobial activity in vitro

The antimicrobial activity of desiccating agent A was evaluated against a dense inoculum (10^{12} CFU/mL) that contained a broad spectrum of pathogens, including gram-negative bacteria (*E coli*, *P aeruginosa*, *T forsythia*, *P gingivalis*), gram-positive bacteria (*S aureus*, *E hirae*), and fungi (*C albicans*). The 50 μL spot of desiccating agent A added to the center of the pool-inoculated plates had significantly reduced growth, with an inhibition ring of $54 \text{ mm} \pm 5 \text{ mm}$ diameter at 24 hours ([Figure 1](#)).

Case series

Ten patients with diabetic leg ulcers ($n = 2$), leg ulcers associated with venous insufficiency ($n = 5$), vasculitic leg ulcers ($n = 1$), revascularized ischemic leg ulcers ($n = 1$), or posttraumatic leg ulcers ($n = 1$) were enrolled in this prospective observational trial. The ischemic leg ulcer on the revascularized leg was not healing at the time of enrollment despite successful revascularization. The demographics of the patients and their wound characteristics are shown in [Table 1](#). The median age of the 10 patients (5 females, 5 males) was 72.5 years (range, 50–90 years). The pedial artery pulses ranged from completely normal ($n = 5$) to present and strongly reduced ($n = 2$) ([Table 1](#)). The duration of the ulcers ranged from 6 weeks to 52 weeks, with a median of 10 weeks and interquartile range (IQR) of 6 weeks and 24 weeks ([Table 1](#)). The median wound bed area was 64 cm² (IQR: 20.5 cm², 110 cm²). The chronic wounds of all patients contained slough over most of the wound bed. The most common prior wound treatments included iodopovidone-soaked gauzes (4/10 patients), silver-containing dressings (4/10 patients), and gentamicin plus betamethasone cream ([Table 1](#)). All patients were followed for at least 6 months after treatment with desiccating agent A.

Immediate effects of desiccating agent A

There were 2 different types of reactions after desiccating agent A application to a wound bed. In 4 cases (eg, [Figure 2](#); case 2), the material present on the wound bed instantly coagulated, and the dried layer was easily, and mostly, removed from the wound bed with saline rinse followed by wiping with a dry gauze. In these cases, desiccating agent A treatment removed the wound material often described as slough and had exposed vital tissue. In the authors' experience, this effect was common in chronic lesions with low-grade inflammation and minimal infection.

The application of desiccating agent A in 6 cases resulted in coagulation and contraction of the material on the wound bed, but the material did not detach with simple rinsing ([Figure 3](#), [Figure 4](#), [Figure 5](#), and [Figure 6](#); cases 3, 4, 7, and 9, respectively). Spot bleeding had appeared throughout the desiccated material in some cases; bleeding was easily stopped with gentle pressure. The authors' impression was that this effect was common in wound beds with robust infections and high-grade inflammation. The surrounding skin in all cases was simply left *degreased* by desiccating agent A treatment and did not show signs of redness, nodules, or vesicles.

Late effects of desiccating agent A

The 1-week visit of 4 patients with wounds left clean by desiccating agent A revealed the presence of mild secretions that were easily removed with saline rinse. These patients did not need or receive an extra application of desiccating agent A. These wounds rapidly evolved to complete granulation on the wound bed. At 6 weeks after desiccating agent A treatment, the status of these 4 wounds was judged to be in the healing phase.

In the 6 wounds in which the desiccated material remained attached to the wound bed, at the 1-week visit, the desiccated material had completely or partially resolved. This effect may be due to reactivation of macrophages. The 6 wounds were judged to be progressing in the healing process at the 6-week endpoint.

In all patients, the desiccated material in the treated wound bed was progressively replaced by granulation tissue. As expected, the wound bed area at 100% full granulation was the same ($n = 5$) or modestly reduced ($n = 5$) in comparison to the basal wound bed area ([Table 1](#)). Median time to reach granulation was 20.5 days (range, 7–78 days) ([Table 1](#)). Interestingly, the median time for males to reach full granulation was shorter (median, 14 days; range, 7–26 days) than that of females (median, 45 days; range, 9–78 days). None of these patients needed an additional application of desiccating agent A; thus, no additional applications were applied.

Side effects and adverse events

Patient-reported transient pain was the only adverse events, and no nodules, welts, blisters, or vesicles were reported. After desiccating agent A application, the patients without concomitant sensory neuropathy ($n = 8$) experienced a burning sensation with a median pain score of 2.5 (IQR: 2, 5) ([Table 2](#)). The pain persisted for a median of 5 minutes (range, 1–180 minutes) ([Table 2](#)). To uncover if a large wound bed area was possibly associated with greater pain intensity, the authors compared the pain reported by the 4 patients who had wound-bed areas greater than or equal to 100 cm² (range, 100–140 cm²). The observations that 2 cases (Cases 7, 9) had reported pain intensity of 7 for 180 minutes whereas 2 cases (Cases 1, 4) reported pain intensity of 2 for 5 and 15 minutes suggested that wound size was not the major determining factor. No association was detected between the wound bed size of the 8 cases and pain.

Discussion

Management of chronic wounds requires multiple strategies that include optimization of wound-bed preparation, concurrent treatment of chronic medical conditions, and consistent follow-up.¹³ Evidence is mounting that the surface material on the chronic wound bed (including extracellular matrix with excessive inflammatory mediators, neutrophils, proinflammatory macrophages, slough, and biofilm) plays a major role in disrupting the wound-healing process and prolongs chronic wounds.^{7,9,11,12} Furthermore, successful removal of biofilm has improved outcomes, reduced cost of treatment,¹² and

prompted consensus recommendations for wound management based on biofilm elimination.^{8,9,21} Desiccating agent A is a novel desiccant that has shown antimicrobial activity against a pool of pathogens common in biofilms of chronic leg ulcers of different etiologies (*E coli*, *P aeruginosa*, *S aureus*),¹⁸ pathogens detected in chronic osteomyelitis of the jaw (*T forsythia*, *P gingivali*),¹⁹ and a common fungal pathogen (*C albicans*). Desiccating agent A resulted in effective debridement of various types of leg ulcers (10/10 patients; 100%). Application of the desiccating agent A was not associated with any serious side effects in this case series, with transient pain lasting from 1 minute to 180 minutes the only issue raised by patients. After desiccating agent A application, 10 of 10 treated leg ulcers proceeded to full granulation without surgical interventions and/or use of advanced medications. In some cases (40%), desiccating agent A treatment facilitated the complete release of the desiccated wound debris by mechanical agitation, whereas the desiccated material in 6 of 10 patients remained attached at 1 or more points. It is possible that desiccating agent A did not completely sever the bridges between the vital tissue and the extracellular matrix layer produced by the inflammatory processes.

This work was prompted by studies of an aqueous phenolsulfonic/sulfuric acid-based agent with desiccating activity in periodontal disease by Italian colleagues^{16,22,23} and a desire to synthesize a less caustic agent. Chronic skin wounds and periodontal infections probably share the involvement of microbiological burden, biofilm formation, and excessive inflammatory proteins as pathologic factors. From these experiences, desiccating agent A appears to effectively denature proteins and extracellular matrix as well as facilitate removal of microbial burden from the wound bed. Although desiccating agent A treatment and mechanical agitation did not completely remove the bioburden from the wound bed in 6 of 10 cases, these wound beds subsequently progressed to 100% granulation in 9 to 53 days. Concurrent inactivation of these risk factors for chronic wounds and their removal may reset the healing process.

Wolcott described the treatment of 3 very challenging, deep chronic wounds with extensive biofilm involvement with a sulfonic/sulfuric acid gel.¹⁷ This desiccating gel was applied after debridement multiple times for each case. Wolcott attributed the restarting and progression of the healing process of the wounds to the distinct gel treatment.¹⁷ Wolcott's gel treatment time on the debrided wound was 5 seconds to 10 seconds,¹⁷ and therefore it was shorter than the 30-second to 60-second treatment time with desiccating agent A of the chronic wound bed that had slough and necrotic tissue. Importantly, desiccating agent A treatment for 30 seconds to 60 seconds was administered without prior debridement.

Cost of treatment of individual wounds by Medicare ranged from \$1138 for a venous insufficiency ulcer to \$3696 for infection diabetic foot ulcer to \$9105 for an arterial-driven ulcer.² This straightforward treatment shows potential for cost reduction of chronic wound management by at least 4 mechanisms: less reliance on surgical debridement, fewer patients requiring systemic antibiotic administration, less risk of allergic reactions, and greater usage of common medicated dressings (eg, sterile soaked gauze).

Limitations

First, although the microbial species in the wound beds were not identified in this study, previous studies suggest that most wound beds of chronic wounds harbor a mixture of microbes.^{11,18} The effects of desiccating agent A on various microbial species are being investigated in animal studies. Second, despite the desiccated inert material remaining on the wound bed initially of some patients, and images immediately following application that may suggest the need for additional debridement, the desiccated material on the wound bed was replaced by 100% granulation tissue. Restarting the healing process by treatment with this desiccating agent A differed from the gold standard of healing in a moist environment. Exploration of its mechanism(s) of action may provide further insight into chronic wounds. Third, although other beneficial effects (eg, less exudation, less redness/inflammation of the surrounding normal skin) of the treatment with desiccating agent A on the wound bed were noticed in this study, these parameters were not formally measured. Fourth, this case series describes desiccating agent A treatment of only 10 patients with leg ulcers of mixed etiologies. It did not include studies on pressure ulcers. However, the major aim of the study was to describe how the new desiccating agent A should be used and its readily observable effects on the wound bed. The net clinical benefit of this new agent, when compared with other forms of debridement, was not the topic of this investigation, but the excellent results obtained in terms of granulation of chronic wounds in this small group of patients supports the design of a subsequent study with additional clinically relevant endpoints. Such a study is currently ongoing.

Most patients experienced transient pain that lasted from minutes to several hours in this series. In subsequent studies, the authors are assessing whether pretreatment of the wound area with lidocaine (5%) containing cream applied for 5 minutes can reduce the pain sensation (data not shown).

Conclusions

Desiccating agent A showed significant antimicrobial activity in vitro against a pool of gram-negative and gram-positive pathogens that are common in chronic wounds and osteomyelitis of the jaw specimens. Desiccating agent A treatment appeared to restart or help restart the healing process of chronic leg ulcers arising from different etiologies, including diabetic

foot ulcer, venous insufficiency ulcer, vasculitic leg ulcer, revascularized ischemic leg ulcer, and posttraumatic leg ulcer. These first observations prompted the authors to design a formal study in which a larger series of patients would be treated.

Acknowledgments

The authors thank K. Molnar-Kimber, PhD, of Kimnar Group LLC for editorial assistance.

Authors: Albert Cogo, PhD¹; Bert J. Quint, PhD²; and Carlo Alberto Bignozzi, PhD³

Affiliations: ¹Villa Berica Hospital, Vicenza, Italy; ²Penta Scientific BV, Amsterdam, The Netherlands; and ³Department of Chemical and Pharmaceutical Science, University of Ferrara, Ferrara, Italy

Correspondence: Alberto Cogo, PhD, Director, Villa Berica Hospital, Vascular Medicine and Diabetic Foot, Via Capparozzo, 10 Vicenza, Vicenza 36100 Italy; albcogo@alice.it

Disclosure: The authors disclose that they are the authors of the patent application for desiccating agent A.

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