Review of local wound management for scleroderma-associated digital ulcers

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ABSTRACT

Digital ulcers (DU) are a common clinical problem in systemic sclerosis (SSc); however, there is no standardization of local wound care protocols for management of these lesions. There is a well-recognized need to develop and standardize non-pharmacological management of DU in patients with SSc, and to adopt these protocols in future clinical trials that focus on DU healing. The purpose of this review is to outline the types of DU that occur in SSc, and provide an update on the principles of wound management for these lesions based on the current literature and expert opinion.

Keywords: Digital ulcers, Systemic sclerosis, Topical treatment, Wound care

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by inflammation, fibrosis and vasculopathy (1). Digital ulcers (DU) are a common complication of SSc affecting 30%-60% of patients (2-4). While there are different possible etiologies for SSc-associated DU, such as traumatic ulceration, which often develops at sites of joint contractures; calcinosis associated lesions; and ischemic DU, which is usually on the digital tip or pulp and are a manifestation of end-stage vasculopathy, determining the activity of ulcerations can be challenging (5-7). The severity and natural history of DU in SSc are affected by disease subtype, disease duration, extent of cutaneous involvement, presence of hand contractures, severity of vasculopathy (often evaluated through assessment of microvascular drop out on nail fold capillaroscopy), and presence of certain auto-antibodies and angiogenesis biomarkers (8-11). The SSc-related DU patient

population is a potentially heterogeneous population and thus, standardizing wound care protocols is crucial. Furthermore, it is important to standardize DU outcome measures, for example, assessments of healing and development of new lesions, during the design phase of DU clinical trials. In general, there is a paucity of evidence on the wound care for managing SSc patients. The purpose of this manuscript is to review the current recommendations for local wound management in patients with ulcerations, which we believe to be applicable to digital ulcers. The overarching goal is to develop recommendations for local wound care for SSc-associated DUs that might be a useful starting point for future clinical trial design.

Role of tissue perfusion in digital ulcer healing

The importance of local wound perfusion in both SSc-related DU development and healing has been demonstrated by flow-mediated dilatation, laser Doppler imaging (LDI) and thermography (12-14). An increase in DU perfusion correlates with healing, and LDI has successfully been implemented as an outcome measure in a clinical trial (15). Similarly, a study investigating power Doppler ultrasonography found that ulnar artery occlusion was a predictor of new or recurrent DUs in patients with SSc (16). Thus, documentation of adequate perfusion by noninvasive measures of blood flow is an important initial step for DU evaluation and may be used both for assessment of severity of vasculopathy as well as likely responsiveness to vasoactive treatments (17).

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Fig. 1 - Digital ulcer debridement.

Importance of vasculopathy in digital ulcer pathogenesis

Decrease in digital perfusion in SSc is related to vasculopathy, which in the hands, manifests with reversible microvascular changes characterized by Raynaud's phenomenon (RP) and nail fold capillary changes (5, 18). With SSc disease progression, severe vasculopathy can progress to more advanced macrovascular injury characterized by critical digital ischemia and gangrene (8, 18). Pathogenesis is related to overproduction of vasoconstrictors by endothelial cells and reduction in endothelium-dependent vasodilatation (5, 18). Most treatment studies for SSc-related DU focus on pharmacologic mechanisms to increase digital perfusion by increasing vasodilatation. However, trials of vasodilators for RP are often not designed to focus on DU as a primary outcome. Assessment of the effectiveness of vasodilator therapy for DU has been limited by small sample sizes, lack of randomization, and inadequate blinding. An additional flaw of most SSc studies to date, is the lack of a standardized local wound care for DU during the lead-in phase. This lack of standardization is not only a potential site-specific confounder, but also limits the ability to use patients as their own controls comparing pre- and post-intervention healing rates (10). A systematic review on non-pharmaceutical treatment modalities for SSc-related DU concluded that larger efficacy studies on treating DU are needed to develop appropriate care guidelines to improve outcomes, promote function, and reduce health-care costs (19).

General principles of wound management

Topical wound care is beneficial as an adjunct to pharmacologic therapies in patients with chronic and immune-mediated wounds. There are no reports available that are specific to SSc patients; however, in patients with wounds associated with autoimmune diseases, the healing process is often arrested in the inflammatory phase (20). Extrapolating from the management of lower extremity ulcers and pressure ulcers, the generally accepted framework for wound management includes wound bed preparation and removal of devitalized tissue; reduction in bacterial load and minimizing inflammation; moisture balance; and promotion of epithelialization

(21, 22). In SSc patients, coexistent pro-thrombotic states (including genetic polymorphisms and antiphospholipid antibody-mediated thrombosis) as well as vasculitis may play a role in ulcer development and should be evaluated (23). While many wound care therapies lack evidence in SSc, dressing changes, debridement, and other wound care activities can be extremely painful for patients, and can become a barrier to compliance with wound care. Thus, reviewing general wound principles and care modalities may improve wound outcomes.

Debridement

Wound debridement is used to remove devitalized tissue and to allow preparation of the wound bed for grafting. Debridement is challenging in all immune-mediated wounds since it carries a risk of aggravating the immune process and further delaying healing. In SSc-related DU, debridement should be used with caution due to poor wound perfusion. However, once gangrene has developed, devitalized wound tissue can contribute to inflammation and exacerbate infection (24), and thus in cases where wet gangrene develops, debridement is recommended (Fig. 1). Collagenase-based ointments are an example of an enzymatic debriding agent that contains clostridial collagenase and other non-specific proteases. Collagenases have been shown to promote granulation tissue formation and re-epithelialization in ischemic wounds in animal models and warrant further study in SSc (25, 26). Some rheumatologists advocate the role of curettage with a scalpel if an eschar is present, cleansing and irrigating by "physiological solution" followed by disinfection by sodium hypochlorite, followed by more "physiological solution" (27); however, this is not a widespread practice.

While wound cleansing is an important component of DU care, there is uncertainty regarding best practice. At present there is no accepted SSc-related DU cleansing protocol. In general, wound cleansing aims to remove debris, including dressing remnants and superficial slough from the wound (28). While irrigation variables including delivery method, volume, and solution additives have not been adequately studied in DU, many providers recommend use of sterile saline based on recommendations from the surgical literature (29). Other cleansing agents used in wound care clinics,

include magnesium sulfate soaks, sodium hypochlorite 0.5% solution, hypochlorous acid solution, and/or antiseptic solutions. They aim to reduce wound biofilm (30-32) but have not been specifically studied in SSc patients.

Topical wound applications

There is currently a paucity of evidence relating specifically to topical applications for SSc-related DU. However, there are several topical therapies with evidence for efficacy in other wound settings, with theoretical benefit in SSc-related DU that are being used in clinical practice. Medical grade honey derived from plants, has been shown to sterilize wounds (33), inhibit biofilm growth (34), and improve healing time in pressure ulcers (35). It is used by some clinicians for treatment of SSc-related DU, but evidence for this practice from clinical trials is lacking. While topical antibiotics, including bacitracin and polymyxin, are options for use on smaller wounds for control of local infection, aminoglycoside-containing products can be a potent sensitizer. The lack of reliable evidence means that it is not possible to recommend the specific topical preparations for SSc-associated DU (36).

Another modality used for the management of chronic wounds, that is beneficial for the population of patients with immune-mediated wounds is MIST therapy. This treatment involves cleansing the wound with a saline spray administered using low-frequency ultrasound. This treatment has been shown to improve ischemic wound healing times when added to standard wound care therapy by disrupting biofilms, increasing vasodilation, growth factor release, and angiogenesis (37). Acoustic pressure wound therapy is a noncontact, low-frequency ultrasound therapy used in combination with a hydrocolloid dressing, which has been reported to reduce pain during DU debridement in SSc (38).

Wound dressings

Wound dressings for SSc-related DU are challenging, in part due to the mechanics of appropriate adherence for small digital lesions, and the lack of published data available. As with other wounds, the ideal dressing must optimize hydration, but also allow exudate management with dressings that have an absorbent effect (21). Polysaccharide biopolymers are slowly becoming popular as modern wound dressing materials because they are inexpensive, naturally derived, absorbent, non-toxic and non-immunogenic, but have not specifically been studied in SSc (39). Dressing changes should occur daily or alternate days, with assessment of wound size in the clinical setting every 1-3 weeks depending on wound progression (40).

Vasodilator therapy for SSc-related DU

While there is a well-recognized need to develop and improve standards of local wound care in SSc (41), oral vasodilator therapies remain the standard for pharmacologic management of SSc-related DU. The European Union League Against Rheumatism (EULAR) (42) and the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) (43) recommend calcium channel blockers (CCB) as first-line therapy for SSc-related RP and DU. There has been some

evidence to suggest that phosphodiesterase-5 (PDE5) inhibitors may be beneficial for DU healing (44), and while a recent randomized controlled trial found that sildenafil did not improve healing time for DU, it did result in fewer overall DUs at 8 and 12 weeks of therapy. This suggests there is some benefit for use of this indication (45). Endothelin-1 receptor antagonists (ETRA) such as bosentan, have the most evidence of benefit on SSc-related DU. The RAPIDS-2 trial was a randomized controlled trial that confirmed that bosentan was associated with a reduction in the number of new DUs, but like PDE5I, did not show an improvement in DU healing time (46). Additionally, prostacyclin analogs have been shown to improve LDI in SSc-related DU (47) as well as possibly prevent the occurrence of new DUs (48). While combination vasodilator therapy may have a synergistic effect, this has not been studied, and randomized and placebo-controlled trials are needed in the SSc population to investigate the impact on prevention and treatment of SSc-related DU. An important aspect of future SSc-related DU pharmaceutical intervention trials will be to ensure standardized wound care cleansing, debridement, topical applications, and dressings in addition to documentation of perfusion of the wound bed.

Surgical procedures

Surgical care for SSc-related DU may include periarterial sympathectomy, but clearly more investigation is needed to best understand standardization of this procedure (49). Chemical sympathectomy via Botulinum A injections is a relatively new therapy that has shown effectiveness in improving SSc-related DU healing in some case series (50); however, randomized control trials have not yet been performed. Regional implantation of autologous adipose tissue-derived cell fractions for treatment has also shown some promise (51) and further research is in progress. Iontophoresis studies of non-invasive transdermal drug delivery based on the transfer of charged molecules using a low-intensity electric current is complex and a potential ancillary modality for SSc-related DU management, but safety may be an issue (52). Another interesting modality is extracorporeal shockwave therapy, which was shown to significantly reduce the number of DUs over 9 weeks from 5.4 to 1.1 in a Japanese Phase 2 study consisting of 9 SSc patients studied for this indication (53).

Pain control

Dressing changes, debridement, and other wound care activities can be extremely painful for patients, and can become a barrier to compliance. There is some evidence available that suggests that better pain control via a variety of modalities can help improve compliance and wound outcomes (54, 55). One study showed that topical lidocaine/prilocaine, either alone or in combination with oral or local morphine prior to debridement, was effective at significantly reducing pain associated with the procedure (55). There is also a case report of two patients where oral oxycodone/naloxone 5/2.5 mg BID was shown to improve compliance and overall wound care in two patients (54). Agents that improve vasodilation can be beneficial, but often there is an initial increase in pain with reperfusion, which patients should be alerted to since otherwise it can result in premature cessation of therapy. There is

some evidence that opioid-based analgesics can adversely impact wound outcomes (56, 57) and thus these agents should be used with caution and adjunctive analgesics should be considered until further SSc specific studies are available.

Ancillary modalities

Education and general lifestyle measures including avoiding fluctuations in ambient temperature, smoking cessation, and stress management are an important aspect of SSc-related RP and DU care (17), and are an important aspect of BSR/BHPR consensus pathway for treatment (43). Addressing biomechanics in SSc-DU wound care is understudied, but it is well recognized that using a multidisciplinary approach, impacts outcomes in wound management of these complex patients. Joint contractures should be managed with aggressive occupational hand therapy to preserve functional outcomes and reduce morbidity in this population (58). The use of patient-reported outcomes that adequately capture the experiences that are most relevant to SSc-related DU patients, are also critical factors to consider in trial design (59).

Conclusion

DUs are a major source of morbidity in SSc, and should be aggressively treated. A comprehensive, multidisciplinary approach to topical wound care in SSc-DU is needed to improve outcomes. A topical wound care approach should include standardized cleansing, debridement, applications and dressings, and incorporate relevant patient-reported outcomes, including pain management. A topical wound care approach should be incorporated into the run-in phase of future SSc-related DU studies, regardless of the treatment modality that is under investigation.

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