Pain

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Background

In systemic sclerosis (SSc), skin ulcers are persistent and often recurrent complications, difficult to manage, slow to heal, and can cause tissue loss [1]. Moreover, these are frequently infected and may lead to osteomyelitis, gangrene, autoamputation, and in some cases septicemia [2, 3].

General principles of ulcer management include the establishment of a clean and healthy wound base, often through surgical debridement, treatment of infection, coverage with an appropriate dressing and maintenance of a moist environment [4].

In SSc, ulcers cause considerable pain with a disabling effect on patients, limiting hand function and daily activities, such as feeding, dressing, and hygiene [5], heavily impairing quality of life [6]. Indeed, the progressive scarring and tissue loss that patients experience daily can lead to some degree of depression and anxiety [7] that has been shown to be a significant predictor of the intensity of pain [8]. Ongoing inflammation and infection may amplify pain experience [8, 9]. Evidence suggests that stress significantly slows wound healing and multiple cellular and biochemical mechanisms have been identified that link to stress and healing [10, 11]. Additionally, pain activates the sympathetic branch of the autonomic nervous system, triggering a physiological response that slows wound healing [12]. Moreover, pain interferes with treatment protocols because patients are unwilling or unable to comply with necessary regimens and protocols. Treatments, like debridement or bandaging, may cause extreme discomfort and noncompliance that significantly delays healing.

Understanding the different types and the neurobiology of pain pathways is a critical step in pain management for SSc patients with skin ulcers.

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Neurobiology of Ulcer-Related Pain

Ulcer-related pain may occur as one or both nociceptive and neuropathic. Nociceptors are the free nerve endings that respond to tissue injury. These nerve endings are either small myelinated A-δ fibers, which conduct pain quickly and produce sharp localized discomfort, or larger unmyelinated C fibers, which conduct pain slowly and are responsible for dull or throbbing pain.

Generally, once damaged tissue has healed, nociceptive pain subsides. If nociceptive pain continues for a prolonged period and the nerve fibers are in a constant inflammatory state – such as with repeated ulcer debridement or dressing changes – sensitization of the nerve fibers may lead to hyperalgesia (amplified pain) [13] or allodynia (pain from a benign stimulus, such as light touch). Allodynia, which is more characteristic of neuropathic pain [14] may confound evaluation and treatment [10].

Neuropathic pain is caused by insult to the actual nerve fibers or central nervous system. It often occurs after prolonged nociceptive pain from an injury, although it may also be caused by inflammation or compression of a nerve by a lesion or scar tissue. Usually it is chronic and described as burning, tingling, or shooting. Unlike nociceptive pain, neuropathic pain often continues even after the tissue has healed because the damaged nerve fibers continue to misfire [10, 14].

The complex neural connections involved in the processing of pain are difficult to understand. The "gate control" theory asserts that a pain stimulus is first regulated in the peripheral nervous system and spine. The dorsal horn of the spinal cord receives nociceptive or pain stimuli from A-δ and C nerve fibers as well as non-nociceptive or sensory stimuli from large A-β fibers. A-β fibers transmit sensory input faster than both A-δ and C fibers. When A-β nerve fibers are simultaneously stimulated with the smaller pain fibers, signals race ahead of the pain transmissions and, by synapsing with inhibitory and projection neurons, "close the

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gate" for transmission of pain stimuli to the brain. This theory would explain why pain is lessened when an injured area is massaged. If only the smaller A-δ and C nerve fibers are stimulated or if an abundance of smaller fibers are stimulated, they inactivate the inhibitory and projection neurons and "open the gate" to the brain [15]. Once nerve fibers have been stimulated, electrical signals are transmitted through the opening and closing of sodium and other ionic channels through the peripheral nerves and ascending pathways and through the spinal cord to the thalamus, hypothalamus, limbic system, and cerebral cortex. Pain transmission of a small A-δ nerve fiber is quickly relayed to the thalamus and cerebral cortex for an immediate response, withdrawal, and pain relief, which occurs through descending pathways. The C nerve fiber travels the same ascending pathway through the spinal cord, only more slowly. In the brain, the signal takes a path through the hypothalamus, which releases certain hormones including those for stress, and the limbic system, which affects emotions. This might explain why chronic pain often is associated with depression and anxiety. Descending pathways originating in the cortex inhibit the ascending pathways in the midbrain and spinal cord, "closing the gate" and diminishing pain perception. Natural opioid neurotransmitters endorphins, dynorphins, and enkephalins are released from the hypothalamus and work to alter pain perception [16].

The pain experience may be changed by anxiety, stress, emotions, and cognition [16]. High levels of anxiety and the release of stress hormones may inhibit descending pathways and "open the gate" causing pain perception to intensify. This explains why individuals experience pain differently and why an individual may respond to the same type of pain differently each time it occurs [12]. Moreover, pain thresholds are largely influenced by previous pain experiences.

Management of Ulcer-Related Pain

Management of skin ulcers requires a multifaceted approach that includes pain control and emotional support at the very outset of treatment. It is necessary to determine the underlying pathology causing the pain. Worsening or change in the type or intensity of pain may indicate a deteriorating condition or impending infection [2].

First, we must differentiate pain by subtypes:

- *Background or chronic pain*: continuous pain stemming from the ulcer itself. This includes pain associated with an infection. Pain levels may fluctuate for background pain over the course of the day due to changes in the wound or whether or not the patient is able to distract themselves.
- *Incident pain*: caused by movement of some kind whether from friction and shear when the patient moves or the movement of the dressing.
- *Procedural cycling pain*: experienced during repetitive procedures like dressing change.
- *Operative non-cycling pain*: operative pain is severe enough to require anesthesia for a procedure like occasional debridement.

It is therefore evident that each of these should be managed at every level of treatment.

Type, intensity, location, and cause of pain must be assessed, as well as the patient physical and emotional status. It is crucial to remember that pain is a complex, subjective, and perceptual phenomenon and pain experience is never in the same way or with the same intensity and responses to treatment modalities vary as well. For this reason, pain management must be individualized.

Non-pharmacological approach is the first line of treatment. Standard topical care treatment includes the maintenance of a warm and humid environment and the application of various medications such as hydrogel, hydrocolloid, paraffin gauze, and antiseptic dressings like silver-coated medications. Healthcare professionals must openly discuss their fears and expectations with patients and encourage them to participate in treatment, such as cleaning or dressing changes. Communication is not only crucial for assessing the state and characteristics of pain but is a way to distract and relax the patient during medications. It is proven that establishing a relationship with the patient helps reduce the level of anxiety and the fear of experiencing procedural or operative pain, thereby allowing to naturally readjust pain perception and raising tolerance to future treatment.

Pharmacological treatment must be targeted according to the subtype of pain. Pain triggers, like infections, ischemia, edema, etc., should be promptly identified and treated.

Local anesthetics must be used for procedural and operative pain; nonsteroidal fast-acting anti-inflammatory drugs can be used for incident or breakthrough pain, while analgesics like paracetamol, NSAIDs or COX-2 inhibitors, cannabinoids, and weak or strong opioids can be used in the control of chronic background pain. Adjunctive therapies, like anticonvulsants, sodium and calcium channel blockers, botulinum toxin injection, or surgical treatments, should be considered if appropriate conservative measures fail.

Take-Home Messages

- Controlling pain at every level of treatment.
- Patients should be encouraged to actively participate in their treatment.
- The primary etiology, size, depth, and extent of skin ulcers help guide treatment.
- All contributing factors should be identified and treated (e.g., ischemia, edema, infections, etc.).

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