Wound treatment and pain management: a stressful time

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Abstract
This review and case study report considers the evidence to indicate that the progress of wound healing is negatively affected by the presence of stressors and in circumstances where patients are in pain. It considers the relationship between perceptions of pain, stress and delayed wound healing with a specific focus on guidance for clinical practice. It is appreciated that although the literature has examined these issues in the management of acute wounds, demonstrating that psychological stress can have detrimental effects on the wound-healing process, the evidence to support this link in relation to chronic wounds is limited. The review considers evidence indicating that punch biopsy wounds heal more slowly in subjects under stress on account of caring for family members with long-term illnesses and also considers briefly the relationship between cortisol secretion in response to stress and the consequent influences on cytokine levels and the wound-healing process.

Introduction
Pain management as part of wound treatment has predominantly targeted acute pain resulting from surgery or trauma. However, pain control has not been a major concern with these wounds because they often heal with few complications. Recently, the incidence of chronic wounds has been increasing, with a rise in the number of diabetic patients and an increase in the ageing population (1). Therefore, it is expected that the incidence of neuropathic pain due to chronic wounds will increase. As a consequence of wound pain, either procedural or pathogenic, patients have been shown to suffer higher levels of psychological stress, and ultimately this stress will have a negative impact on the healing process (2). In addition, pain control has been shown to have significant cost implications; therefore, reduction in pain and stress should be implicit in any treatment regimen of chronic wounds (3). This article identifies the evidence for the relationship between pain, stress and delayed healing, with a specific focus on guidance for clinical practice.

Pain management related to wound treatment
Pain during wound treatment cannot be ignored. An investigation of quality of life (QoL) revealed that pain management was the highest priority among patients with chronic wounds (4). Therefore, the European Wound Management Association (EWMA) focused exclusively on wound treatment and published a position paper entitled ‘Pain at wound dressing changes’ in 2002 (5). The paper reflected on the...
time when patient-centred outcomes such as minimising pain were given scant attention. In 2003, the campaign for raising awareness regarding ‘wounds and pain’ started in earnest with a special issue on pain in a supplement of Ostomy Wound Management (6). Furthermore, at the second World Union of Wound Healing Societies (WUWHS) meeting held in 2004, a consensus document – ‘Minimising pain at wound dressing-related procedures’ – was published, developing into a worldwide awareness campaign (7). Following this, Principles of Best Practice introduced in this article were prepared for the third WUWHS meeting in 2008 to address this important topic (8).

**Meaning of pain**

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (9). Physiologically, pain is a biological warning system to protect the body from noxious stimuli. However, it is a subjective experience that can affect individuals in different ways. As a result, pain is often considered to be a negative phenomenon.

**Differentiating between chronic and acute wound pain**

The firing threshold for perception of pain is decreased in chronic wounds due to repetitive stimulation by inflammatory mediators in these types of wounds. This can cause strong pain with only slight nociceptive stimuli during wound treatment (primary hyperalgesia), leading to situations where the treated patient’s protestations are perceived as ‘immature’ or evidence of ‘over-reacting’. An apparently normal-looking periwound region can also be hyperalgesic (secondary hyperalgesia), and even mild stimulation, such as that caused by peeling off an adhesive dressing, may cause unbearable pain. Because non-nociceptive stimuli, such as pressure and contact, which would not normally cause pain, may cause pain (allodynia), abrasive clothing or even a slight air current caused by people’s movement may be perceived as pain. If vessels that nourish nerves are damaged due to peripheral arterial disease, neuropathic pain, in addition to nociceptive pain, in the wound area can occur (10).

Dressing changes can be painful, unpleasant and stressful if aggressive adhesive dressings are used. If, in addition to this, the patient has increased sensitivity to pain, then it may make the procedure excruciating. Subsequently, anxiety and depression may occur as a result of associated psychological stress. Therefore, health care professionals involved in wound care need to consider chronic and acute wound pain separately and be aware that chronic pain is not just a prolonged form of acute pain. If the mechanism is different, management of the pain should be different as well. Therefore, the two forms of pain should not be confused and must be acknowledged during wound treatment to prevent complex pain.

**Psychological stress and chronic wounds**

This article reviews the literature reporting on the relationship between stress and delayed healing of chronic wounds, with specific reference to the role of pain as a significant contributor to psychological stress. In particular, the anticipation of pain at dressing removal and wound cleansing is explored. The literature to date clearly demonstrates that psychological stress can have detrimental effects on the wound-healing process with respect to acute wounds; however, evidence to support this link in relation to chronic wounds is limited.

**Contributing factors to wound-related pain**

In both clinical practice and academic research, it is important to recognise that pain is a multifaceted experience with a number of contributing influences, including psychosocial and physiological factors (11). Pain is a significant problem for patients with all types of wounds, contributing to considerable levels of suffering and distress and consequent reductions in QoL (12). Dressing removal, wound cleansing, debridement, microbial damage and inappropriate dressing selection can all contribute to wound-related pain. However, it has been demonstrated that dressing removal and wound cleansing are often reported as the most painful experiences associated with wound management (8). Not only is pain an unpleasant experience that needs to be minimised, but it may also have a negative impact on wound recovery.

**The relationship between pain and psychological stress**

Pain is an unpleasant sensory and emotional experience contributing to patients’ psychological stress and other negative emotional states such as anxiety, fear and depression (11). Heightened anxiety can, in turn, decrease a patient’s pain threshold and reduce pain tolerance (13). The perception of pain is influenced by psychological, emotional, cognitive and social factors, as well as learned behaviours, for example, patients might make social comparisons with other patients to evaluate their own condition (14). It has been suggested that stress plays a role in the perception of pain, for example, under conditions of high stress, the anticipation of pain at dressing removal may lead to an increase in pain intensity (15).

**Stress, endocrine response and the immune system**

The term ‘stress’ often refers to the consequences of the failure of the human body to respond appropriately to emotional or physical threats (16). Physiologically, prolonged stress can lead to raised levels of the hormone cortisol. Although stress is not the only reason that cortisol is secreted into the bloodstream, it has been termed ‘the stress hormone’ because it is secreted at higher levels during the body’s ‘fight or flight’ response to stress (17). Higher and more prolonged levels of cortisol in the bloodstream have been shown to have negative effects on the body, including increased heart rate, higher blood pressure and lowered immunity and inflammatory responses in the body.

**Psychological stress and delayed wound healing**

As a consequence, depression in immune function and changes to the levels of various inflammatory cytokines and enzymes
involved in tissue repair, for example, a reduction in the levels of cytokines involved in tissue repair, result in delayed wound healing. Changes in these cytokine levels could therefore offer a plausible explanation of how reduced rates of wound healing occur with pain-induced psychological stress (17).

A number of studies have suggested a link between psychological stress and delayed wound healing. For example, a review of the scientific literature revealed that psychological stress is associated with slower or delayed wound healing in stressed older adults, adults with chronic wounds and surgical patients (18,19).

A large proportion of the research into psychological stress and delayed wound healing has been demonstrated using biopsy wounds. To emphasise that minimising psychological stress can promote faster wound healing, a recent study showed that volunteers who had been inflicted with biopsy wounds and asked to disclose a traumatic and upsetting event of the wound when compared with a control group who had been asked to write about time management (20).

In a study investigating the potential benefit of implementing stress-management interventions during the wound-healing process, the results showed that individuals exhibiting lower levels of anger control were more likely to be categorised as slow healers and exhibit higher cortisol reactivity during administration of the biopsy wound. The observed increase in cortisol secretion was, in turn, related to a longer time to heal (21). These findings suggest that the ability to regulate the expression of anger has a clinically relevant impact on wound healing. Mild stress experienced as a result of academic examinations has also been shown to have significant consequences for wound healing (22). Students took an average of 3 days longer to completely heal a biopsy wound during examinations (40% longer). In addition, production of interleukin-1β declined by 68% during examinations, providing evidence of one possible immunological mechanism.

In addition, Ebrecht et al. (23), also using a punch biopsy model, suggested a considerable negative influence of stress on wound healing and proposed that elevated cortisol levels, rather than health behaviours (i.e. alcohol consumption, exercise, healthy eating and sleep influences), play a role in this effect.

In a study investigating long-term, naturally occurring, psychological stress caused by caring for a relative with Alzheimer’s disease, an experimental group of 13 women caring for relatives with the disease was compared with a control group after receiving a punch biopsy on the non-dominant forearm. It was found that caregivers reported significantly more stress than controls, and wound healing took an average of 9 days longer in caregivers than controls (17).

Psychological stress and postsurgical healing

More relevant is to investigate the clinical situation, for example, wound healing as a critical outcome in surgery (19,21). Poor healing can result in wound infections or complications, as well as prolonged hospital stays, increased patient discomfort and delayed return to activity (19). In a study by Holden-Lund (24), stress-management techniques demonstrated that surgical patients had significantly less anxiety, lower cortisol levels (1 day following surgery) and less surgical wound erythema than the control group. Similarly, in a study by Broadbent et al. (19), it was found that greater pre-operative stress significantly predicted lower levels of interleukin-1 in the wound fluid. Greater worry about the operation predicted lower levels of matrix metalloproteinase-9 in the wound fluid as well as more painful, poorer and slower recovery. Taken together, the findings of the studies exploring post-surgical healing suggest that psychological stress and anxiety is detrimental to the wound-healing process. Consequently, this needs to be taken into account when managing the pre- and post-operative aspects of treatment. Although these studies of biopsy and surgical wounds are supportive of the notion that psychological stress can delay wound healing in acute settings, it is not possible to elucidate the role of stress in chronic wounds from these studies. Indeed, evidence of the relationship between psychological stress, pain and chronic wound healing is limited, and most of the evidence for a causal link between psychological stress and wound healing comes from studies of acute wound healing (16). Moreover, chronic wounds do not follow the same healing pattern as acute wounds, and it is not clear whether reductions in immune function and changes in levels of pro-inflammatory cytokines as a result of psychological stress follow the same pattern in chronic wounds as in acute wounds (16).

Stress, chronic wounds and delayed healing – supporting evidence

Despite the limited literature in this area to date, the findings of the following studies provide empirical support for the relationship between psychological stress and delayed healing in chronic wounds. A study conducted by Jones et al. (25) explored the prevalence of anxiety and depression in 190 patients with chronic venous leg ulceration across nine Trusts in North West England. The results showed that the two symptoms that appeared to be most associated with anxiety and depression were pain and odour. It was concluded that psychological factors, including anxiety and depression, should be a focus in the assessment and review of patients with chronic leg ulceration.

Cole-King and Harding (18) also examined the relationship between the healing of chronic wounds and anxiety and depression. Their findings showed the relationship to be statistically significant, with delayed healing being associated with a higher mean Hospital Anxiety and Depression Scale (HADS) score ($P = 0.03$), demonstrating that depressive and anxiety symptoms were associated with chronic wound healing. The findings of these studies exemplify that interventions, in addition to clinical wound treatment, would benefit the healing process by minimising the patients’ levels of pain, psychological stress and anxiety. Every clinician should make a point of paying attention to psychosomatic aspects in the diagnosis and therapy of chronic wounds (14). In the case of some individual patients, adjuvant psychological treatment may serve to improve QoL, relieve subjective distress and possibly also support wound healing itself (14). Therefore,
practitioners need to take into account the fact that stress plays a part in wound healing, particularly in leg ulceration.

More recently, Upton et al. (2) demonstrated that patients with chronic wounds and high levels of procedural pain, measured by visual analogue scale (VAS), have correspondingly high levels of stress. The implications of procedural and chronic wound pain were also evaluated in a Delphi study, which demonstrated that use of inappropriate dressings was one of the major causes of high levels of pain (26). A pain ladder was identified with corresponding levels of treatment for procedural pain, for example, low-level pain (VAS 1–3) might be treated by paracetamol. Alternatively, high levels of pain (VAS 7–10) might be treated with opioids and/or administration of anaesthesia with Entonox, adding considerably to resource use and cost. In some cases, patients might have to be admitted to hospital when changing dressings due to the procedure is so painful (26).

**Case studies**

The following case studies identify how pain and consequently stress has been alleviated in a variety of situations.

**Case 1**

The patient was a 62-year-old male, who was diagnosed as having type 2 diabetes mellitus at the age of 52. He started maintenance haemodialysis at the age of 60 because of chronic renal failure. Three months before his first visit to our clinic, gangrene developed from wounds on the first and fifth toes of the right foot. The patient’s former physician had amputated the tip of the right first toe and the right fifth toe at the base of the proximal phalanx. The patient’s stump became infected with methicillin-resistant *Staphylococcus aureus*, in addition to redness and swelling of the entire foot. Consequently, he was referred to our clinic.

Examination at the first visit showed that the right first toe was gangrenous on the dorsal aspect of the distal phalanx and up to the base of the proximal phalanx on the plantar side. Necrotic tissue was present at the tip of the right second toe. The right fifth toe had been amputated at the level of the base of the proximal phalanx; redness and fluctuation due to subcutaneous abscess were detected between the stump and the medial plantar region. The patient experienced severe pain [8 on the numeric rating scale of 0 (no pain) to 10 (worst pain ever), Figure 1A].

The dorsal skin perfusion pressure (SPP) was 35 mm Hg, and the plantar SPP was 31 mm Hg. It has been claimed that SPP values >35 mm Hg are a reliable predictor of wound-healing outcomes (27). Before treating local infections, we conducted endovascular catheterisation for the treatment of the peripheral vascular disease, one of the major causes of the chronic wounding, to promote wound healing.

![Figure 1](image-url)

**Figure 1** (A) Gangrene on the dorsal aspect of the distal phalanx of the right first toe and up to the base of the proximal phalanx on the plantar side. Necrotic tissue can be seen at the tip of the second toe. The fifth toe had been amputated at the level of the base of the proximal phalanx; redness and fluctuation due to subcutaneous abscess was detected between the stump and the medial plantar region (arrow). (B) Incision of the reddened area between the base of the fifth toe and the medial plantar region reveals abscess located along the plantar muscles (arrow). (C) Tissue lost by surgical debridement had to be replaced by granulation to eliminate dead space. (D) At 1 year and 9 months after surgery. After wound healing, the patient wore orthopaedic shoes. No wound recurrence has been observed.
Selective approaches to wound debridement include autolytic, enzymatic, biological, physical, surgical and wet-to-dry methods. Major types of pain associated with different types of debridement strategies have been described (8). In our case, surgical debridement was chosen to treat the wound extending from the amputation site of the fifth toe to the medial plantar region. Incision of the reddened region revealed an abscess located along the plantar muscles (Figure 1B).

After surgical debridement, the VAC® Therapy System (Kinetic Concepts Inc., San Antonio, TX) was applied to promote granulation and eliminate dead space (Figure 1C). We amputated the first toe at the metatarsophalangeal joint and the second toe at the proximal interphalangeal joint.

When the depth of the wound floor decreased as a result of granulation, treatment with the VAC® Therapy System was terminated, and the wound was managed with regular dressings. The patient’s pain was alleviated because of improvement in local infections (3 on the 0–10 numeric rating scale). However, we anticipated that use of conventional dressing materials would cause significant pain because the wounds had become chronic.

The stratum corneum that constitutes the outer surface of the skin acts as a barrier to protect deeper tissue. The corneocyte has natural moisturising factors that are involved in skin hydration (28). Dykes et al. (29) attached to the forearm five types of adhesive dressings that had been painted with dye and investigated how much dye came off when the dressing was removed. The authors (30) also attached various types of adhesive dressings to the forearm and stained the corneocytes in the stratum that adhered to the dressing to allow quantification. The degree of removal of corneocytes by peeling the dressing was found to vary greatly and the importance of dressing selection for the treatment of chronic wounds was recognised. For this reason, we selected soft silicone dressings, as in our clinical experience, these prevent trauma to the wound or to the surrounding skin at the time of removal. The pain observed during treatment with the VAC® Therapy System remitted. Eventually, the patient’s wound healed completely. After healing, the patient wore orthopaedic shoes, and no wound recurrence was noted (Figure 1D).

**Case 2**

The patient was a 73-year-old female. She had a cerebral infarction at the age of 68, resulting in left-hand side hemiplegia. During a 1-year period, starting 2 years before her first visit to our clinic, the patient underwent endovascular catheterisation three times for the treatment of peripheral arterial disease, the cause of the rest pain of the right lower extremity. After the fourth catheter treatment, performed 1 year before the first visit, the patient developed wounds on the fourth and fifth toes of the right foot. A fifth catheter treatment was performed in an attempt to improve blood circulation and heal the wound, but it yielded no major improvements. On the contrary, the patient developed a wound on the right second toe. A sixth catheterisation was attempted but was aborted due to no run-off to the plantar arteries. Instead, autologous peripheral blood mononuclear cell transplantation was performed (31). Because the wounds became worse and the pain intensified, she was referred to our clinic after a seventh catheter treatment.

At her first visit, an ulcer was noted on the dorsal side of the middle phalanx of the right second toe (Figure 2A). On the plantar aspect of the right fourth toe, necrosis extended to its base. Necrotic tissue was seen at the tip of the right fifth toe. The patient’s pain was severe (8 on the 0–10 numeric rating scale).

At the time of the first visit, 1 year had elapsed after the onset of wounding. During this period, the patient developed contact dermatitis at the wound sites due to exudates and medical adhesive tapes used to attach gauze. In addition, chronic dermatitis was observed over the entire right foot. The patient was administered steroid ointment to treat the dermatitis (Figure 2B).

Pain signals are transmitted through the peripheral nerves to the spinal cord and muscle tension increases with the excitation of reflex motor nerves. The sympathetic excitation contracts the blood vessels, causing increased metabolism in the muscles and localised reduction in blood flow, leading to ischaemia in the tissue. Pain-causing substances (e.g. prostaglandins) released from hypoxic tissue further stimulate the peripheral nerves and spinal cord, causing a vicious cycle of pain that inhibits wound healing (10).

Neuropathic pain is difficult to control with non-steroidal anti-inflammatory agents alone, routinely used for acute pain. Gabapentin, which is one of the calcium channel α2δ ligands, has an analgesic action because it increases the function of the γ-aminobutyric acid neuronal system (one of the descending pain inhibitory systems) and suppresses the release of excitatory neurotransmitters (glutamate) at the terminal of nociceptive primary neurones (10). This case was characterised by strong wound pain, hyperalgesia and allodynia for which the patient was given gabapentin.

Treatment with steroid ointment and gabapentin considerably reduced pain (5 on the 0–10 numeric rating scale). We administered pre-emptive analgesia before foot surgery, as intense pre-operative anxiety and pain are known to elicit a higher level of postoperative pain (32). The dorsal and plantar SPP values measured after the seventh catheterisation were 12 and 15 mm Hg, respectively. Although foot angiography showed no blood flow in the dorsalis pedis artery (Figure 2C), vascular connection was found between the plantar artery and the arterial network on the dorsum of the foot (33), which suggested that partial toe amputation would be sufficient for healing.

Consequently, the patient underwent amputation of the second and fourth toes through the diaphysis of the proximal phalanx and that of the fifth toe through the distal phalanx. Healing of the wounds led to remission of the pain (Figure 2D).

**Conclusions**

The article in the position document ‘Pain at wound dressing changes’ issued by EWMA in 2002 (11) stated the following: ‘... That there is a physiological basis to such chronic pain may be seen as a welcome finding to the sufferer; for
too many carers, both lay and professional alike, there is often a difficulty in believing that which cannot be directly observed...’ Health care professionals involved in wound treatment tend to focus only on the wound and believe what they can observe. However, one must not forget that in chronic wound treatment, the patient’s agony and anticipation (psychological stress) are hidden within things that cannot be observed. This is summarily expressed in the last principle of the WUWHS consensus statement: Health care providers should ensure wound-related pain control for every patient (8), thus maximising their treatment in line with guidelines while also reducing the potential for greater cost implications for treating pain and stress.

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