The American Journal of Surgery®

The American Journal of Surgery 188 (Suppl to July 2004) 31S–35S

Practical treatment of pain in patients with chronic wounds: pathogenesis-guided management

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Abstract

In addition to its own inherent morbidity, the pain associated with chronic wounds presents a primary obstacle to healing. To initiate safe and effective therapy, we used a multidisciplinary approach that required the wound-healing clinician and pain-management practitioner to work together to diagnose and treat the pain associated with these wounds. This approach emphasizes wound pathophysiology, which facilitates treatment modalities that focus on the cause of the pain as well as more efficient analgesia. All wound patients were approached with the assurance that they should not experience pain. The most important part of pain control is objective assessment and assuring patients that their pain will be resolved. Differential diagnosis is critical (eg, wound pain associated with infection, necrosis, spinal cord injury, neuropathy). We determined that to resolve pain, the following 4 goals must be achieved: (1) removal of all nonviable, locally infected tissue and elimination of all cellulitis; (2) determination of wound pathogenesis; (3) availability of both local and systemic analgesia; and (4) assessment of objective improvement through the periodic use of an analgesic scale. By following this protocol, the wound-healing clinician can expect decreased length of hospital stay and resolution of pain in nearly all patients with wounds.

Our integrated team approach to treatment of wound pain involves specialists from both the wound-healing and pain-management teams. This approach allows for a comprehensive evaluation and strategy in managing the patient's painful wound. Based on this approach, guidelines derived from the 10 most common causes of chronic wounds were established for treating pain [1] (Table 1). Ischemia, tissue damage, and neuropathy represent the 3 broad etiologies of the pain in patients with chronic wounds. For each of these etiologies, we constructed a general pain management proposal based on correcting pathologic causes of the chronic wound. Case histories, representative of our experience in thousands of cases of wound and pain management, illustrate our basic pain treatment strategies for chronic wounds resulting from ischemia, tissue damage, and neuropathy. Our multidisciplinary approach alleviated pain for almost all the patients treated by our team.

Ischemic wound pain management

Case history

An 86-year-old woman with a 20-year history of arterial insufficiency experienced sharp pain in the posterior aspect of her left lower extremity, associated with blanching erythematous lesions over her toes. The pain worsened with walking and subsided with rest. She had a left lower-extremity revascularization procedure 10 years before the current presentation. She was under the care of the vascular surgeon on the wound team, who assessed that she was not a candidate for angioplasty or further bypass. The patient rated her pain as 10/10, on a scale where 10 was the worst pain she could imagine. The pain disrupted her sleep, and she took ibuprofen to no avail.

The patient was started on tramadol, and 10-mg nortriptyline was prescribed at bedtime for sleep and analgesia. A

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This work was supported in part by the United Spinal Association and by Grant No. DK059424 from the National Institutes of Health.

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doi:10.1016/S0002-9610(03)00289-7

Table 1
Causes of pain in the 10 most common chronic wound etiology

Chronic Wound Etiology	Cause
Arterial insufficiency	Ischemia
Sickle cell disease	Ischemia
Venous stasis disease	Tissue damage
Infection	Tissue damage
Pressure	Tissue damage
Obesity	Tissue damage
Steroids	Tissue damage
Chemotherapy	Tissue damage
Radiation	Tissue damage
Diabetes mellitus	Neuropathy/ischemia

series of left lumbar sympathetic nerve blocks was performed to provide analgesia and increased blood flow to the lower extremity.

Case discussion

Ischemic wounds are mainly caused by arterial insufficiency secondary to vaso-occlusive disease (eg, arteriosclerosis) or vasospastic disease (eg, Raynaud phenomenon). Pain management of these wounds focuses on treating the underlying ischemia to relieve the pain.

Sympathetic nerve blocks are relatively noninvasive modalities for increasing regional blood flow to an area of ischemia. Sympathetic nerve inhibition produces smooth muscle dilation of the arterioles and venules, decreases peripheral resistance, increases capillary flow, and, secondarily, increases skin capillary oxygen tension and saturation. This effect of a "nonoperative microvascular bypass" provides a collateral blood flow to areas not amenable to surgical bypass procedures. Sympathetic blockade can be performed at several anatomical levels. Epidural anesthesia by way of percutaneous catheters, with diluted concentrations of local anesthesia, provides differential sympathetic blockade while maintaining motor function. Tunneling of the catheter allows long-term usage or home use.

A more regional sympathetic block would theoretically decrease the chance of the "steal phenomenon," which shunts blood away from ischemic areas. A lumbar sympathetic percutaneous block, on an ambulatory basis under local anesthesia with fluoroscopic guidance, is used frequently for lower-extremity ischemia. This block reduces motor dysfunction, hypotension, and vascular "steal." For longer-lasting results, neurolytic agents [2] or radiofrequency lesioning can be performed.

Spinal cord stimulation also blocks sympathetic output at the spinal cord level and is used in those cases refractory to less invasive techniques [3]. The procedure increases regional blood flow, promotes local wound healing, and is accomplished by placing electrodes in the epidural space posterior to the dorsal columns of the spinal cord. Thus, use of sympathetic blocks, by whatever means, increases lower-extremity blood flow and decreases pain. Analgesia is obtained by correcting the underlying physiologic causes of ischemic pain.

Oral analgesics (eg, nortriptyline and tramadol) also were used in our case study to supplement the primary injection treatment. Nortriptyline is a tricyclic antidepressant with sleep-promoting properties and has analgesic effects that arise from actions on the descending inhibitory spinal cord pain pathways. Nortriptyline exhibits fewer anticholinergic side effects than other tricyclics, such as amitriptyline, and is therefore better tolerated (especially by elderly patients). Tramadol provides analgesia by weakly binding to opiate receptors, as well as analgesic effects similar to tricyclic antidepressants, at the spinal cord level. It has fewer side effects than either the opioids or tricyclics and, consequently, is efficacious as an as-needed analgesic, especially for elderly patients.

Tissue damage wound pain management

Case history

The following history is representative of any nonparalyzed patient with a venous ulcer or pressure ulcer:

A 33-year-old, 325-lb man with non–insulin-dependent diabetes mellitus (NIDDM) and a 5-year history of venous reflux and ulcer in his right lower extremity had a large, painful, irregular ulcer located superior to the medial malleolus. It was surrounded by hyperpigmented skin with classic dermatitis. The patient described sharp, burning, itching pain that was constant and further exacerbated at night. He was taking a cyclooxygenase-2 (COX-2) inhibitor (a nonsteroidal anti-inflammatory drug [NSAID]) and acetaminophen with codeine for the pain, which provided mild relief with some associated nausea.

This patient was then started on an extended-release opioid (fentanyl patch), an anticonvulsant (gabapentin), a tricyclic antidepressant (amitriptyline), and as-needed tramadol for the pain. He continued taking the COX-2 inhibitor.

Case discussion

This patient had venous reflux and a painful leg ulcer. Venous ulcers are usually secondary to reflux between the deep and superficial lower-extremity venous systems. The reflux leads to increased venous pressure, venous dilation, increased capillary permeability, and extravasation of fluid and proteins. Ultimately, tissue damage and skin breakdown occur and an ulcer develops. Tissue damage stimulates the release of chemical mediators of inflammation-sensitizing peripheral somatic pain receptors, instigating transmission of pain from the area.

Pain management for tissue-damage wounds relies on systemic analgesics. A protocol based on the guidelines of the World Health Organization (WHO) analgesic ladder is used. This protocol advocates a tiered approach by which

less potent medications are instituted first, until the patient is comfortable and experiences minimal side effects. When lower tier drugs prove ineffective, the next higher tier medications are added to the regimen in a stepwise fashion. First-tier medications include nonopioids, such as NSAIDs and tricyclics. Second-level medications include drugs with opioids in combination with acetaminophen or NSAIDs. Third-tier medications include all other opioids, both short and long acting [4]. By using combinations of medications—for example, opioids, NSAIDs, tricyclics, and sometimes anticonvulsants—that act on different parts of the pain pathway, an additive/synergistic effect can be achieved. Fast-onset, short-duration medications (frequently opioids) are added to treat episodic breakthrough pain.

This patient had a painful venous ulcer with the possible addition of diabetic or ischemic neuropathic pain. His pain was not controlled adequately on first- and second-tier analgesics from the WHO ladder. Therefore, we developed a chronic analgesic regimen for him with an extended-release opioid fentanyl patch. The patch provided continuous release of the opioid transdermally, and the medication was maintained at steady analgesic blood levels, maximizing analgesia and minimizing side effects. The slow-release mechanism of the fentanyl transdermal delivery system (changed every 72 hours) facilitates patient compliance and provides safe delivery of a potent analgesic. It also is associated with less nausea. The COX-2 inhibitor, NSAID, desensitized peripheral nociceptors (pain receptors), and a tricyclic antidepressant stimulated descending inhibitory tracts in spinal-cord pain pathways, which diminished the sharp, shooting aspect of his neuropathic pain. An anticonvulsant may be effective either at the peripheral or central nervous system level and, therefore, it also was used for neuropathic analgesia. The anticonvulsive decreased abnormal firing that contributes to the burning sensation of neuropathic pain. To diminish breakthrough pain, the patient was treated with tramadol as required. Tramadol has opioid and tricyclic effects, and is beneficial to treat both the somatic tissue-damage pain and neuropathic pain.

Neuropathic (diabetic) wound pain management

Case history

A 47-year-old, 300-lb man with a 5-year history of NIDDM had a 10-month history of bilateral foot pain and ulceration. He described the pain as sharp and shooting in character, intermittent, and worse at night. A 1-cm ulcer was noted on the medial aspect of his right hallux, as well as blanching erythema on the medial aspect of the left hallux. Sensory examination demonstrated that diminished feeling was present in the distal distribution of L5 bilaterally. Putting pressure on his feet while walking was extremely painful. The patient was taking carbamazepine and gabapentin for neuropathic pain, as well as Coumadin (warfarin sodium; Bristol-Myers Squibb, Princeton, NJ) for cardiomyopathy.

We initially started this patient on amitriptyline and oxycodone/acetaminophen as needed, in addition to the carbamazepine and gabapentin. Oxycodone was effective in relieving pain, but its duration is short. Thus, he was given extended-release oxycodone and a lidocaine patch over the areas of neuropathic foot pain.

This patient required a series of lower-extremity intravenous Bier blocks with bretylium and lidocaine, a series of bilateral local anesthetic lumbar sympathetic blocks, and ultimately required bilateral radiofrequency-lesioning lumbar sympathetic blocks.

Case discussion

This patient had bilateral diabetic neuropathic pain with an ulcer caused primarily by pressure or injury. The pain followed a dermatomal distribution and was lancinating in nature, which indicated an injury to a somatic nerve. Hyperesthesia (an exaggerated response to stimuli) and allodynia (a painful response to nonpainful stimuli) are frequent findings in these types of patients. Pain can even occur in areas of sensory deficit, known as anesthesia dolorosa.

Neuropathies are caused by axonal degeneration and segmental demyelination. Patients with diabetes develop ischemic neuropathy secondary to microvascular changes in the vasa nervosum, the blood supply to the nerve itself. Ischemia to the nerve selectively leads to a greater loss of large inhibitory fibers (eg, $A\beta$) than small stimulatory pain fibers (eg, $A\delta$ and C). This differential injury increases pain sensation from the periphery. Changes at the levels of the dorsal root ganglia, dorsal horn neurons, and brain itself also have been associated with neuropathic pain [5].

The most well-established and most extensively studied class of medications used to treat neuropathic pain are the tricyclic antidepressants. They inhibit serotonin and norepinephrine in the descending inhibitory pain tracts of the spinal cord. Amitriptyline has been studied extensively for treating neuropathic pain [6], but desipramine [7] and nortriptyline also are effective with fewer anticholinergic side effects.

Currently, anticonvulsants are probably the most commonly used medications to treat neuropathic pain. The first anticonvulsants shown to be effective in treating neuropathic pain were carbamazepine [8] and diphenylhydantoin [9]. However, they both have a long list of side effects, so newer anticonvulsants, with far fewer complications, have virtually replaced them. Gabapentin, a newer-generation anticonvulsant, also has been shown to be effective in multiple types of neuropathic pain, including diabetic neuropathy [10].

Other classes of medications used to treat neuropathic pain with varying success include mexiletene [11], capsaicin [12], *N*-methyl-D-aspartate (NMDA) inhibitors [13], clonidine [14], tramadol [15], and lidocaine patches [16].

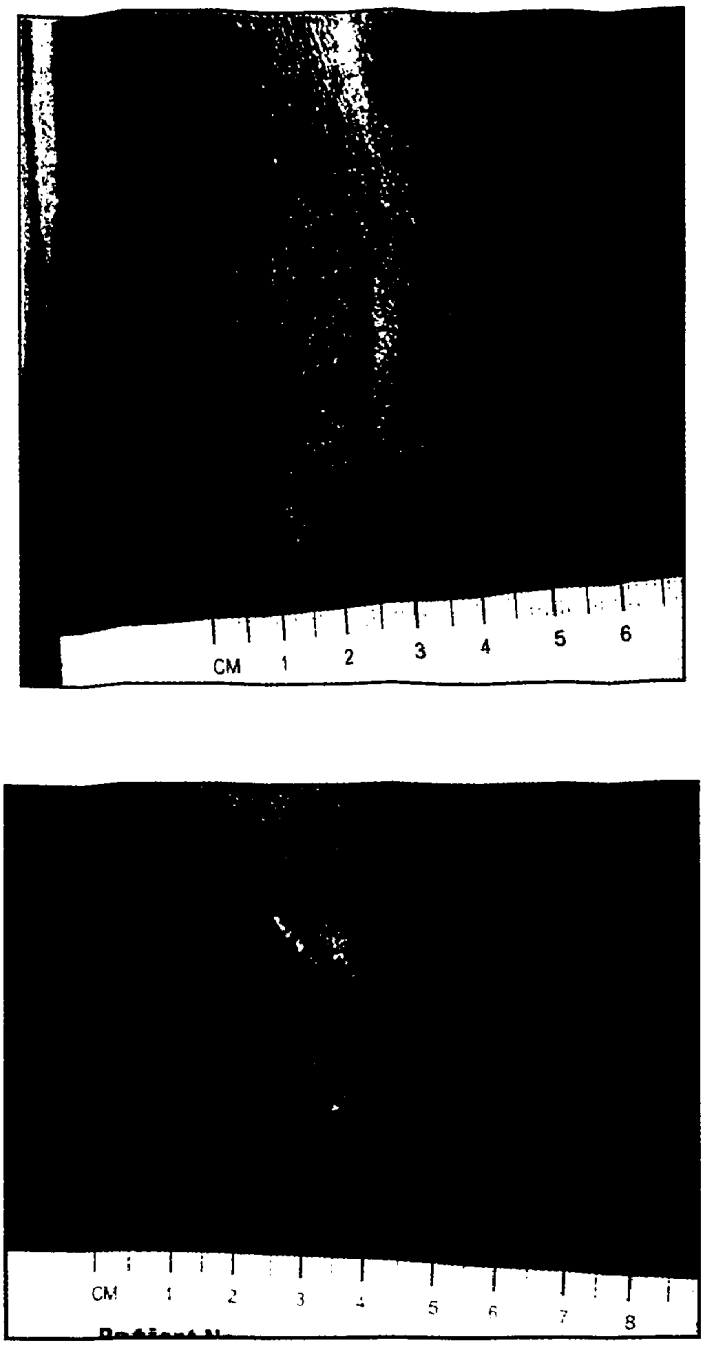

Fig. 1. This patient presented with excruciating pain that resulted in loss of sleep. (*Top*) The nonhealing wound located at a fracture site. This wound slowly closed using topical cadexomer iodine. A lidocaine patch was also used and resulted in a significant reduction in this patient's pain. (*Bottom*) The healed wound. A typical example of where a wound physician and pain physician collaborated to ensure comprehensive treatment that resulted in both wound closure and resolution of pain. In this case no debridement or culture of wound was needed.

Opioids use to treat neuropathic pain are somewhat controversial. Clinically, analgesia is obtained with higher than "usual" dosages, which risks excessive side effects. NSAIDs provide systemic analgesia for neuropathic pain as part of a chronic analgesic regimen but probably should be avoided in anticoagulated patients.

Also controversial is the use of sympathetic blocks for diabetic neuropathic pain. The basis of this treatment relates to microvascular stenosis, which causes ischemic neuritis. Sympathetic blockade should improve this pathological situation. The described patient received Coumadin. Therefore, the injection of choice included a regional lower-extremity intravenous Bier block with bretylium, a sympatholytic agent, and lidocaine (a local anesthetic) to avoid deep injections. When the series of Bier blocks failed to provide sustained relief, a series of local anesthetic and, ultimately, neurolytic radiofrequency-lesioning lumbar sympathetic blocks were undertaken, after the patient's Coumadin was stopped and the prothrombin time returned to normal. Bretylium Bier blocks have a sympatholytic action and decrease the release of catecholamines from terminal nerve endings. Lumbar sympathetic blocks inhibit sympathetic transmission at the level of the sympathetic ganglion. Using bretylium Bier blocks and lumbar sympathetic blocks together may be synergistic.

Epidural anesthesia by way of a percutaneous catheter may be considered in patients with bilateral neuropathic disease but was not used in this patient because of the anticoagulation. Anticoagulation is a relative contraindication for central axis injections. If sympathetic blocks are considered, Coumadin should be stopped 4 days before the procedure and a prothrombin time obtained to ensure adequate hemostasis.

Summary

The most efficient analgesia is obtained by treating the underlying pathophysiology that causes the pain [17,18]. This requires an understanding of the mechanisms of pain and an understanding of all the different modalities available to correct this pathophysiology. As demonstrated in Fig. 1, the wound-healing practitioner and pain-management expert must be in constant communication; each must have a basic knowledge of the other's specialty to provide optimum care and reduce morbidity.

The critical factor in wound-pain management is first to ascertain whether surgical debridement is necessary to clean the wound and promote healing, and then to find the most effective combination of topical and systemic analgesia. All pain, regardless of cause, can be objectively diagnosed and treated. The patient should be assured that treatment efficacy will be objectively measured and the analgesic treatment modified to obtain the best results.

References

[1] Freedman G, Cean C, Duron V, Tarnovskaya A, Brem H. Pathogenesis and treatment of pain in patients with chronic wounds. Surg Technol Int 2003;11:168–179.

[2] Cousins MJ, Reeve TS, Glynn CJ, Walsh JA, Cherry DA. Neurolytic lumbar sympathetic blockade: duration of denervation and relief of rest pain. Anaesth Intensive Care 1979;7:121–135.

[3] Mingoli A, Sciacca V, Tamorri M, Fiume D, Sapienza P. Clinical results of epidural spinal cord electrical stimulation in patients affected with limb-threatening chronic arterial obstructive disease. Angiology 1993;44:21–25.
[4] World Health Organization. 1986 Cancer Pain Relief. Geneva: World Health Organization; 1986.
[5] Myers RR. 1994 ASRA Lecture: the pathogenesis of neuropathic pain. Reg Anesth 1995;20:173–184.
[6] Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37:589–596.
[7] Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250–1256.
[8] Rull JA, Quibrera R, Gonzalez-Millan H, Lozano Castaneda O. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia 1969;5:215–218.
[9] Ellenberg M. Treatment of diabetic neuropathy with diphenylhydantoin. N Y State J Med 1968;68:2653–2655.
[10] Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA 1998;280:1831–1836.
[11] Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet 1988;1:9–11.
[12] Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Diabetes Care 1992;15:159–165.
[13] Rabben T, Skjelbred P, Oye I. Prolonged analgesic effect of ketamine, an *N*-methyl-D-aspartate receptor inhibitor, in patients with chronic pain. J Pharmacol Exp Ther 1999;289:1060–1066.
[14] Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage "enriched enrollment" design. Pain 1995;60:267–274.
[15] Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology 1998;50:1842–1846.
[16] Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. Clin J Pain 2000;16:S62–S66.
[17] Brem H, Jacobs T, Vileikyte L, et al. Wound-healing protocols for diabetic foot and pressure ulcers. Surg Technol Int 2003;11:85–92.
[18] Brem H, Balledux J, Bloom T, Kerstein MD, Hollier L. Healing of diabetic foot ulcers and pressure ulcers with human skin equivalent: a new paradigm in wound healing. Arch Surg 2000;135:627–634.