

Wound Healing: The Next Millennium

Unresolved issues remain, but new therapies are emerging for the treatment of diabetic foot ulcers.

BY MADHURI REDDY, MD, FRCPC

As we enter the next millennium, and advanced therapies have not worked as well as anticipated, it is important to revisit the fundamental pillars of chronic wound care as well as look forward to new treatments. In approaching the patient with a diabetic foot ulcer, clinicians should seek to treat the cause, apply local wound care and address patient-centered concerns.¹

Treating the cause includes a multifaceted approach to treating diabetes. Tight glycemic control is crucial, with HbA1c as an indicator. Target blood pressure and lipid goals should be set and met, and patients should be counseled to have an annual ophthalmology visit as well as an annual measure of renal function. Physicians need to work with patients to develop an exercise program, control weight and offer advice regarding smoking cessation.

The acronym VIPS should be kept in mind when treating the cause of a diabetic foot ulcer. V = vascular, I = infection, P = pressure offloading/downloading, and S = sharp surgical debridement.

VASCULAR DIABETIC FOOT ULCERS

Microscopic distal surgery is a treatment option for vascular diabetic foot ulcers. Recent studies have examined popliteal-to-distal bypass for limb salvage as well as dorsalis pedis artery bypass.^{2,3} Recent research has also shown some success with gene therapy for the treatment of vascular causes of diabetic foot ulcers. Researchers reported injecting rabbits with a version of a peripheral vascular disease gene-carrying molecule.⁴ The gene successfully activated vascular endothelial growth factor (VEGF). In addition to stimulating new vessel growth and improving perfusion in the damaged leg tissue, the treatment also appeared to prevent apoptosis of living muscle cells starved of blood supply.

When treating a diabetic foot infection it is important to be aware of bacterial balance. A superficial wound may be nonhealing, have exuberant

granulation, excessive exudates and size and slough. As it becomes deeper, the infection may be warm and tender, painful, have erythema >2 cm and probes to the bone.

PRESSURE OFFLOADING/DOWNLOADING

To alleviate pressure on the diabetic foot ulcer, offloading or downloading with a total contact cast (TCC) may not be an option because they may not be readily available.

TCCs are not useful with ischemia, are not useful with deep infection and are not useful for heel ulcers. Alternatives must be considered, such as Coban wrap-around pneumatic walkers and gel inserts.

SHARP SURGICAL DEBRIDEMENT

Table 1 shows the relationship of debridement to healing in a 1996 study.

In a *Cochrane Database of Systematic Reviews*,⁵ five randomized controlled trials (RCTs) of debridement were identified. Three of the trials assessed the effectiveness of a hydrogel as a debridement method, one evaluated surgical debridement and one evaluated larval therapy.

When the three hydrogel trials were pooled, results suggested that hydrogels are significantly more effective than gauze in healing diabetic foot ulcers (absolute risk difference

TABLE 1. RELATIONSHIP OF DEBRIDEMENT TO HEALING

	Placebo	PDGF
Center 1	19% debrided 10% healed	15% debrided 20% healed
Center 6	87% debrided 25% healed	81% debrided 83% healed

Source: Steed, DL, 1996

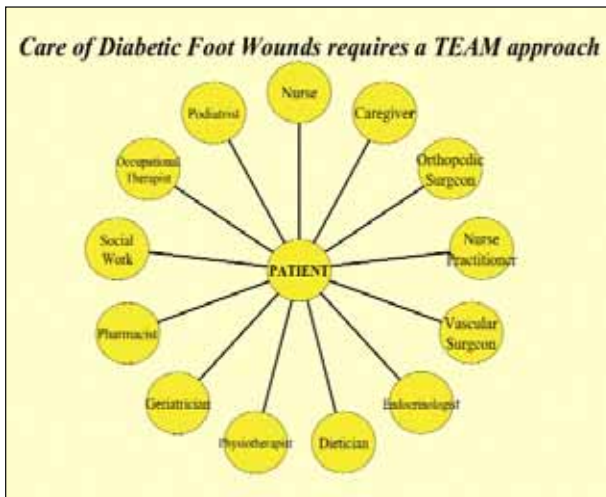


Figure 1. Care of diabetic foot wounds requires a team approach.

0.24; 95% CI: 0.10, 0.36).

Surgical debridement and larval therapy showed no significant benefit in these small trials. Other debridement methods such as enzyme preparations or polysaccharide beads have not been evaluated in RCTs of people with diabetes.

While there is evidence to suggest that hydrogel increases the healing rate of diabetic foot ulcers, more research is needed to evaluate the effects of a range of widely used debridement methods and of debridement per se.

PATIENT-CENTERED CONCERNS

Concerns that focus on the patient include pain treatment and depression. Although a number of drugs are commonly used to treat neuropathic pain, the only drugs specifically approved for that use are: carbamazepine for the treatment of trigeminal and glossopharyngeal neuralgias; gabapentin for the treatment of postherpetic neuralgia; and duloxetine for the treatment of painful diabetic neuropathy.

The clinical characteristics of painful neuropathies may include: burning that most commonly affects the distal extremities; paroxysmal shooting or lancinating pains or musculoskeletal cramping; allodynia, hyperalgesia or hyperpathia; pain in a diurnal pattern, usually worse at night; and paresthesias described as feelings of tightness, swelling of the hands or feet, or walking on cobblestones.

A physical examination often reveals distal sensorimotor deficits and vasomotor cutaneous changes in case of autonomic involvement.

TREATMENT OPTIONS

Tricyclic antidepressants (TCAs) may be used to treat painful neuropathies. The first-generation TCAs include amitriptyline, imipramine and doxepin. Nortriptyline, a sec-

ond-generation TCA, has fewer side effects and has demonstrated better results in the elderly. The efficacy of these drugs has been demonstrated in many RCTs. Their antineuralgic properties are independent of their antidepressant properties.

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) can also be used.^{6,7} While SSRIs may not be as effective as TCAs, they are better tolerated. Studies have shown the SSRIs paroxetine (Paxil, SmithKline Beecham) and citalopram (Celexa, Parke-Davis) to be somewhat better than placebo.

The SNRI venlafaxine (Effexor, Wyeth) was studied in a double-blind, randomized, placebo-controlled, multicenter, parallel group trial that randomized 244 adult outpatients with painful diabetic neuropathy. Patients were randomized to placebo, 75 mg or 150 to 225 mg of venlafaxine extended-release. The 75 mg/day was a no-effect dose. The dose range of 150 to 225 mg/day showed significant pain improvement (50% improvement in weekly pain scores) compared to placebo (27% in weekly pain scores).

At a dose of 75 mg/day, venlafaxine is a relatively selective inhibitor of serotonin reuptake; however, at higher doses it additionally inhibits the reuptake of norepinephrine and dopamine.

Another antidepressant used for the treatment of painful neuropathies is bupropion.⁸ It is a non-TCA with a better side-effect profile.

The use of carbamazepine in trigeminal neuralgia was evaluated in three double-blind, placebo-controlled, crossover design trials that included a total of 151 patients. Pain was improved compared to placebo. In two double-blind, crossover trials for use in diabetic neuropathy it was better than placebo, but not better than TCAs. It was not useful for the treatment of the constant burning pain of postherpetic neuralgia but was effective in treating the lancinating pain component in this condition.⁸

In two large clinical trials, gabapentin was found to be effective as a symptomatic treatment for postherpetic neuralgia. Its use in diabetic neuropathy is still questionable. When compared to amitriptyline it had similar efficacy, and the most common side effects were somnolence and dizziness.⁸

Some topical agents may offer relief from painful neuropathy. Capsaicin is a product extracted from hot chili peppers. It depletes substance P from the terminals of unmyelinated C fibers, initially causing a burning sensation followed by anesthesia. Randomized data for this product is conflicting. Lidocaine gel and patches have been shown to provide significant short-term partial pain relief for neuropathic pain in three double-blind trials. EMLA, or eutectic mixture of local anaesthetics, lidocaine and prilocaine has also been used. A meta-analysis (6 trials/ 317 patients) showed a statistically



Figure 2. Clinicians must treat the cause, provide local wound care and address patient-centered concerns.

significant reduction in debridement pain scores versus placebo for venous stasis ulcers.

In general, it is agreed that treatment with topical agents leads to mild or moderate improvement at best, and it is not effective as the sole therapy for neuropathic pain.

RCTs for opioids in diabetic neuropathy have shown statistically significant improvement in pain compared with placebo, but no improvement over TCAs.^{9,10} There are more dropouts from opioid groups than from TCA or placebo groups.

Although opioids have demonstrated efficacy in RCTs of neuropathic pain, this class of drugs should be reserved for the management of refractory patients and after treatment with other therapies have failed. However, opioid therapy is frequently necessary for adequate treatment.

CHRONIC PAIN, DEPRESSION SIMILAR

Chronic pain and depression share common neurochemical pathways. The mean prevalence of pain in depressed patients is 65%, and the mean prevalence of major depression in pain patients is 52%. The more pain complaints a patient has, the more likely the patient is to be depressed. Inattention to pain can cause refractoriness to depression treatment, and not addressing depression can preclude successful pain treatment. It is important to keep a proper moisture balance to ensure wound healing. Maceration has a negative effect on healing.

Wound bed preparation came about because advanced therapies did not work as well as we thought. One advanced therapy is Promogran (Johnson & Johnson),¹¹ a collagen and oxidized regenerated cellulose combination that inactivates matrix metalloproteases (MMPs). In a RCT trial of 276 patients, it was found to be comparable to mois-

tened gauze. Promogran plus silver has also been used.

Rimon Therapeutics has a product that may be available within a few months. MI-Gel works by binding MMPs. It consists of two polymers, including beads of Rimon's MI Theramer suspended in ThermoGel, a thermosensitive gel that is liquid at room temperature and gels at body temperature. The dressing is applied as a liquid, which then gels to the wound and can be removed with cool water without pulling or sticking to the wound or damaging new tissue.

Another therapy is topical negative pressure (TNP) for treating wounds. A *Cochrane Database of Systematic Reviews* looked at RCTs – two small trials of 34 participants. One considered patients with any type of chronic wound and the other considered patients with diabetic foot ulcers only. The two small trials provided weak evidence suggesting that TNP may be superior to saline gauze dressings in healing chronic human wounds.⁵ However, due to the small sample sizes and methodological limitations of these trials, findings must be interpreted with extreme caution. The effect of TNP on cost, quality of life, pain and comfort was not reported. It was not possible to determine the optimum TNP regimen.

The care of diabetic foot wounds requires a team approach (Figure 1). Clinicians must treat the cause (Figure 2), provide local wound care and address patient-centered concerns. Local wound care consists of debridement, a bacterial balance and moist interactive healing. A nonhealing wound must be considered carefully and biological agents may be appropriate avenues to consider. ■

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