Trials in Neuropathic Diabetic Foot Ulceration

Time for a paradigm shift?

Diabetic foot ulceration is a serious and expensive complication with considerable morbidity that affects up to 15% of diabetic patients during their lifetime; moreover, ~80% of amputations are preceded by foot ulcers (1). Despite these facts, Mason et al. (2) concluded in their systematic review of treatments for foot lesions that the evidence base for treatments is poor. Furthermore, they criticized the majority of published trials of potentially promising treatments for neuropathic ulcers as being small, inadequately powered, and failing to use standardized methods and outcomes.

It is therefore refreshing to read the work of Kalani et al. (3) in this issue of *Diabetes Care*. In a well-designed controlled trial, patients with neuroischemic ulcers were randomized to receive daily subcutaneous low–molecular weight heparin (LMWH) or placebo. Those randomized to LMWH had significantly better outcomes with respect to healing rates and amputation. There are also potentially exciting new treatments for ischemic limbs in diabetes (4,5). Therapeutic angiogenesis with vascular endothelial growth factor and other factors appears promising in chronic limb ischemia, and larger trials are now in progress.

Unfortunately, evidence of the efficacy of new dressings and other potentially promising local treatments for neuropathic foot ulcers is not so forthcoming. It is well recognized that neuropathy is the most important contributing cause of diabetic foot ulceration (6), which frequently combines with deformity and trauma to result in ulceration. It is generally accepted (7) that a neuropathic ulcer will heal if three factors are attended to: *1*) the circulation is intact, *2*) infection is treated appropriately, and *3*) repetitive pressure is mitigated in the region of the ulcer. Arterial inflow is, by definition, not a common problem in neuropathic ulcers, and treatment of present infection, using appropriate antibiotics, can be achieved in most cases. Most trials have failed to appreciate the importance of the last of these principles, forgetting that neuropathic patients lack pain sensation and, despite all good intentions, tend to walk on plantar ulcers. Therefore it is hardly surprising that new trials of therapeutic agents have been disappointing if patients fail to wear the provided removable off-loading orthoses or cast walkers.

Is there evidence to support this failure to wear prescribed off-loading devices? The answer is clearly yes, and several published studies demonstrate this. First, when supplied free of charge with specialist footwear, Knowles et al. (8) reported that only 20% of patients actually wore the shoes. Second, Armstrong et al. (9) recently assessed activity patterns of neuropathic diabetic foot ulcerations managed with an off-loading removable cast walker (RCW). By recording activity using a computerized pedometer and comparing this with activity recorded from a similar device implanted in the RCW, it was shown that the RCW was only worn during 28% of daily activity (9). Third, in a randomized controlled trial (10) of different off-loading devices, we clearly demonstrated the superiority of the total-contact cast (TCC) over a half-shoe or RCW in the management of neuropathic plantar foot ulcers. As a previous study (11) had confirmed that the TCC and RCW reduced pressure to a similar extent, it can be concluded that in the randomized off-loading trial (10), those patients randomized to the RCW did not wear the walker for all of their walking time.

Finally, a recent trial of a promising new dressing surprisingly failed to demonstrate efficacy. Veves et al. (12), in an adequately designed and powered study, compared Promogran with standardized moistened-gauze therapy, but were unable to show a difference in healing rates. A likely explanation for this outcome could be the failure to standardize off-loading, which was "left to individual centers."

In consideration of the above, we propose a paradigm shift in the design of clinical trials for new treatments for plantar neuropathic ulcers. To permit any new therapy to demonstrate efficacy, should future trials not employ a nonremovable off-loading device? This regulation has not been applied because of concern over the use of TCCs, which require considerable expertise and time to use and can themselves injure the insensate foot. We recently described (13) an alternative to the TCC, the instant TCC, using an RCW made nonremovable by wrapping it with cohesive bandage and/or plaster. This has several potential advantages over the traditional TCC. First, it enforces compliance but is lighter in weight. Second, it is quicker and easier to apply than the TCC, removing the need for a highly trained casting technician to be available at every clinic. Finally, it can reduce costs, because the same RCW can be used throughout the treatment. There are a number of randomized trials in progress that are using the nonremovable RCW; when its efficacy is proven to be similar to the traditional TCC, surely all future trials of therapy should use a nonremovable off-loading device.

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