Systemic therapy for leg ulcers

Sir,

The article venous leg ulcer: Systemic therapy by B Nair[1] was very well-written. Systemic therapy for leg ulcerations is usually only supportive to the central theme of management, as has already been brought out by the author very succinctly. Since these are adjuncts to other treatment, there is bound to be an overlap between this article and the one titled “other treatments.” The reader is urged to go through that article and the corresponding letter to the editor for a holistic view.

Nutritional supplements have already been covered extensively. Of value is a quick mention of magnesium. This micronutrient functions as a cofactor in enzymes required for protein and collagen synthesis, and is used in some topical wound healing applications. However, as with zinc, its use as a supplement in the general surgical population lacks proven benefit.[2]

The principle for the use of venoactive drugs in chronic venous insufficiency associated with leg ulcer is to improve venous tone and capillary permeability, although the precise mechanism of action of these drugs is not known. Flavonoids have venotonic properties and act on leukocytes and endothelium, resulting in decreased inflammation and permeability, thus reducing edema.[3] A meta-analysis of randomized prospective studies using micronized purified flavonoid fraction as adjunctive therapy found that venous leg ulcers healed more rapidly.[4]

Pharmacotherapy with the exception of pentoxifylline does not benefit venous ulcer healing. Cilostazol (a Type III phosphodiesterase inhibitor) reduces pain and increases walking distance in intermittent claudication, but is not recommended for the treatment of arterial ulcers.[5] A Cochrane review[6] evaluated eight trials on intravenous naftidrofuryl for critical limb ischemia. The drug was not effective in reducing the symptoms.

Indications for antibiotic therapy and optimal treatment regimens are ill-defined. Most published guidelines are based on expert opinion rather than evidence-based consensus. Without proven benefit and in the absence of evidence, misuse of systemic antibiotics may place patients at unnecessary risk for significant adverse side effects and may contribute to the increasing emergence of antibiotic

resistance.[7] In chronic wound infection, systemic antibiotics should only be used for the treatment of sepsis, osteomyelitis, cellulitis, lymphangitis, abscess formation, or in the presence of other signs of invasive tissue infection. A recent Cochrane review of antibiotics for chronic venous ulcer concluded that current evidence does not support the use of systemic antibiotics to treat venous leg ulceration.[8] There is evidence that systemic antibiotics are needed only if the patient has features of sepsis in the form of fever, leukocytosis, and quantitative wound biopsy with $>10^5$ organisms per g of tissue.

Currently, routine use of aspirin is without proven benefit in the treatment of leg ulcers. As has been brought out by the authors, levamisole and mesoglycans may have some role to play in healing leg ulcers. Defibrinating agents have not been shown to improve healing of ischemic ulcers or to reduce the number of amputations.[9]

The use of reduction of inflammation with drugs such as doxycycline and nonsteroidal anti-inflammatory drugs, has been studied in animal models and considered for clinical use. However, no substantial clinical data are available to suggest that these agents are beneficial for accelerating the healing of chronic wounds, especially in leg ulcers.

Systemic therapy may be of value in ulcers due to uncommon etiology. Prednisolone, cytosporine, intravenous gamma globulin, methotrexate, and azathioprine may be of value in vasculitic ulcers. In pyoderma gangrenosum, apart from steroids that remain the first line of treatment, immunosuppressants such as cyclosporin A, mycophenolate and azathioprine, dapsone, and cytokine blockers like tumor necrosis factor alfa monoclonal antibody. Ulcers due to necrobiosis lipoidica may respond to short-term glucocorticoid treatment with aspirin, dipyridamole, and cyclosporine showing variable results. Leg ulcers in the tropics, principally caused by infectious agents, may either be tropical phagedenic ulcer, veldt sore, Buruli ulcer or erythema induratum (Bazin's nodular vasculitis). They may respond to systemic antibiotics if warranted.[10]

A word about stem cells, the current rage, merits special mention. Systemic injections of granulocyte colony-stimulating factor can mobilize stem cells from bone marrow into the peripheral blood and then to the wound site. This may increase accumulation of collagen and may promise excellent results in terms of wound bed preparation and healing, especially in the leg ulcer.[11] Numerous animal studies and a few pilot studies in human wounds have shown that bone marrow-mesenchymal stem cells (MSCs) can augment wound closure. Still, the primary contribution of MSCs to cutaneous regeneration and the long-term systemic effects of MSCs are yet to be established. In addition, we need to determine whether other types of stem/progenitor cells will be more effective. Therefore, more randomized controlled clinical trials need to be undertaken.[12]

Systemic therapy for leg ulcers can at best be considered adjunctive. The wound care provider is cautioned to determine possible adverse effects of these drugs conscientiously weigh the risk-benefit ratio and act judiciously.

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