Adjunctive treatment for leg ulcers

Sir,

The article venous leg ulcers: Other treatments by I Majid[1] was revealing. Leg ulcers are a therapeutic challenge. Many important facets integral to the treatment of leg ulcers have been covered extensively in the issue by various authors. The basic principles of treatment are to remove or treat precipitating causes; compression therapy to promote healing continues to be the cornerstone in effective treatment of the leg ulcer, especially the one with venous etiology. Apart from that for venous ulcers, leg elevation, multi-layered dressings, and surgical management help; for arterial ulcers, smoking cessation, revascularization, antiplatelet medications, pentoxifylline, and management of risk factors are of benefit; for neuropathic ulcers, off-loading of pressure, topical growth factors, and tissue-engineered skin may be of value; for pressure ulcers, off-loading of pressure, reduction of excessive moisture, sheer, and friction with adequate nutrition may be key to success. Diabetics may further benefit from improved glycemic control to reduce ulcer risk.[2] Glycemic control may also reduce the risk for amputations in patients with preexisting ulcers. The goal in diabetic foot ulcer treatment is complete wound healing. Standard wound care consists of debridement, infection control, offloading through total contact casting, and dressings to maintain a moist wound bed.

Many adjunctive measures help in enhancing healing of the leg ulcer. Systemic therapy with hyperbaric oxygen or intravenous therapy with agents such as prostaglandins, local mechanical therapy such as negative pressure wound therapy (NPWT), electromagnetic stimulation or enhanced local oxygen therapy, topical therapy with vaso-active growth factors such as platelet-derived growth factor or tissue-engineered skin and skin products are the cutting-edge technological advancements for healing of the leg ulcer. A lot of other techniques and modes of treatment are anecdotal and individualized, and, therefore, cannot be covered fully in the present issue of leg ulcers. The author has very lucidly discussed the commonly used adjunctive modalities namely electrical stimulation, hyperbaric oxygen therapy (HBOT), NPWT, and laser therapy. A brief mention of nutrition, ultrasound therapy, and stem cells too merit a mention in this letter to the editor, to complement the comprehensive subject of adjunctive therapies for the treatment of leg ulcers.

Therapeutic ultrasound therapy and electrical stimulation are fast becoming very promising clinical tools for chronic wounds. The use of electrical stimulation for wound healing allows the clinician to deliver exogenous electrical signals into wound tissue, thereby mimicking the natural underlying bioelectrical response to injury. Interestingly, electrical stimulation is also being used for skin graft salvage.[3] In recent years, low-frequency (kilohertz) ultrasound devices have increasingly been used for wound healing, serving as debriders or as healing promoters.[3] Randomized controlled trials of low frequency, noncontact ultrasound treatment suggest an effect on neuropathy and superficial diabetic foot ulcers, with some evidence of benefit in ischemic ulcers.[4,5] Two kinds of action of ultrasound are of particular interest for the wound

care specialist: Debridement and modulation of the healing process. These two actions are achievable using two distinct types of device; contact ultrasound devices are debriders, particularly effective for the treatment of eschar or inflammatory tissue as well as for the debridement of painful ulcers, and the noncontact ultrasound devices have been shown to clinically affect the healing process at various phases, particularly in neuropathic diabetic foot ulcers and to a certain extent in ischemic leg ulcers.[3]

As has already been highlighted, HBOT causes oxidative stress brought about by hyperoxia that can have beneficial therapeutic effects in wound healing. Currently, HBOT is an expensive modality but is cost-effective for the limb and the life-threatening problem of infected diabetic foot ulcers. The challenge for the wound care providers is to develop data that elucidate its cost-effectiveness in other states of impaired wound healing such as late effects of radiation to the skin, compromised grafts and flaps, and reperfusion injuries.[6]

The authors have very vividly and extensively dealt with mechanism and applications of NPWT, a modality that had a tremendous impact on the field of wound healing in the past decade and a half. A special mention should be made of its role in temporizing the management of the leg ulcer and even healing it. Over the sole of the foot, especially in the diabetic, it is of value to help wound healing by secondary intention as compared to skin graft application. This prevents recurrent breakdowns and ulcerations over skin grafts that will be thinner than normal skin and, therefore, more prone to inadvertent trauma. 125 mm Hg may no longer be considered the optimal negative pressure and can give rise to more complications such as pain and bleeding. It is preferable to use 75-100 mm Hg pressure, either in the continuous or intermittent mode. It should also be understood by the reader that VAC is a patented item manufactured by KCI, and thus, the term cannot be freely used to interchange with NPWT.

As the authors have very appropriately put across, efficacy of lasers in the management of venous ulcers has not been proven till date. Indeed, there are very few studies on the subject and none in the recent past.

Nutrition has an important role to play in wound healing. Arginine increases wound collagen synthesis and thus, may help in wound healing. Use of fish oil supplements rich in omega-3 fatty acids adversely impacts the healing response. How long before surgery such supplements should be stopped to reverse the impact on wound healing is not known.[7] Vitamin C deficiency, in addition to impairing wound healing, has also been associated with an increased susceptibility to wound infection. The recommended dietary allowance for Vitamin C is 60 mg/day but in surgical patients, the dosage varies widely. Burn victims may require as much as 1-2 g/day to restore urine and tissue levels to normal. There is no evidence to suggest that high doses of ascorbic acid are of any benefit to wound healing in nondeficient states; conversely, there is no evidence that excess Vitamin C is toxic.[8] Vitamin A deficiency impairs wound healing. Administered either topically or systemically, it reverses the anti-inflammatory effect of corticosteroids on wound healing. Vitamin A has also been proposed as therapy for wound healing impaired by diabetes, malignancy, cyclophosphamide, or radiation. In the severely injured, doses of Vitamin A as high as 25,000 IU/day (5 times the recommended daily dose) have been advocated and used without any significant side effects. Larger doses of Vitamin A do not improve wound healing further, and prolonged excessive intake can be toxic. The anti-inflammatory properties of Vitamin E are similar to those of steroids. Vitamin A can reverse the wound healing impairment induced by Vitamin E.[7] Of the numerous trace elements present in the body, copper, zinc, and iron have the closest relationship to wound healing. Copper strengthens the collagen framework. Zinc is the most well-known element for wound healing. Zinc levels can be depleted in severe stress and patients receiving long-term steroids. In these patients, both Vitamin A and zinc supplements improve wound healing. The current recommended daily allowance for zinc is 15 mg. Severe iron deficiency can result in impaired collagen production. As part of the oxygen transport system, iron can affect wound healing but this only occurs in severe iron deficiency anemia. Hypovolemia, rather than specific levels of hemoglobin, has been shown to adversely affect wound healing, most likely by decreasing oxygen and nutrient delivery to the healing wound site. Herbal supplements such as garlic, ginseng radix rubra, curcumin, and ginger extract have been shown to influence wound healing.[7]

Mesenchymal stem cells have been shown to enhance wound healing through increased angiogenesis, re-epithelialization, and granulation tissue formation. Lee *et al*. recently demonstrated that adipose-derived stromal cells, under hypoxic conditions such as wound healing, are capable of high proliferative rates, enhancing repair with increased release of angiogenic factors, such as vascular endothelial growth factor and basic fibroblast growth factor.[9] The discovery that both bone marrow-derived mesenchymal stem cells and adipose-derived stromal cells support the formation of blood vessels under hypoxic conditions encourages further research into the cells' therapeutic potential. Stem cells have enormous potential for skin tissue regeneration, as the cells can both regenerate lost tissue and promote wound repair through paracrine co-ordination of their actions. Diverse cell types such as embryonic stem cells, mesenchymal stem cells, resident tissue stem cells (such as epithelial stem cells), and induced pluripotent stem cells are currently under intense investigation.[10] Stem cells enhance the concept of tissue engineering to generate bioengineered skin for replacement

therapy as well. The cells can be derived locally (e.g. fibroblasts, keratinocytes, melanocytes, adipocytes, hair follicle cells, and skin progenitor cells) or systemically (e.g. cells in the bone marrow system). Studies indicate that progenitor cells produce more favorable outcome than differentiated keratinocytes in bioengineered skin.[9]

The foregoing adjunctive measures may improve many aspects of wound healing in the patient with a leg ulcer. Excitingly, stem cells, especially adipose-derived stromal cells, may be of immense value in healing leg ulcers in the future. The world waits with bated breath for more trailblazing research on the subject and its diverse clinical applications.

Vijay Langer

Department of Plastic Surgery, Army Hospital Research and Referral, New Delhi, India

Address for correspondence:
Prof. Vijay Langer,
Department of Plastic Surgery, Army Hospital Research and Referral, New Delhi - 110 010, India.
E-mail: vlangz@gmail.com

REFERENCES

1. Majid I. Venous leg ulcers: Other treatments. Indian Dermatol Online J 2014;5:383-85.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217-28.
3. Ennis WJ, Lee C, Plummer M, Meneses P. Current status of the use of modalities in wound care: Electrical stimulation and ultrasound therapy. Plast Reconstr Surg 2011;127 Suppl 1:93S-102.
4. Ennis WJ, Foremann P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: Results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage 2005;51:24-39.
5. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound: The Mayo clinic experience, 2004-2006. Adv Skin Wound Care 2007;20:221-6.
6. Thom SR. Hyperbaric oxygen: Its mechanisms and efficacy. Plast Reconstr Surg 2011;127:131S-41.
7. Kavalukas SL, Barbul A. Nutrition and wound healing: An update. Plast Reconstr Surg 2011;127 Suppl 1:38S-43.
8. Rivers JM. Safety of high-level Vitamin C ingestion. Ann N Y Acad Sci 1987;498:445-54.
9. Lee EY, Xia Y, Kim WS, Kim MH, Kim TH, Kim KJ, *et al*. Hypoxia-enhanced wound-healing function of adipose-derived stem cells: Increase in stem cell proliferation and up-regulation of VEGF and bFGF. Wound Repair Regen 2009;17:540-7.
10. Ko SH, Nauta A, Wong V, Glotzbach J, Gurtner GC, Longaker MT. The role of stem cells in cutaneous wound healing: What do we really know? Plast Reconstr Surg 2011;127 Suppl 1:10S-2.

Access this article online

Quick Response Code:

Website: www.idoj.in

DOI: 10.4103/2229-5178.142563