Venous leg ulcer: Systemic therapy

Brijesh Nair

Department of Dermatology and Venereology, INHS Sanjivani, Kochi, India

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Address for correspondence:
Dr. Brijesh Nair, Dermatologist, INHS Sanjivani, Kochi - 682 004, India.
E-mail: meshugah12@rediffmail.com

SYSTEMIC THERAPY IN VENOUS LEG ULCERS

The classification of systemic therapeutic options for treatment of venous leg ulcers (VLUs) are mentioned in Table 1.[1] The value of systemic therapy is to act as an adjuvant to compression therapy and local ulcer care, when compression alone fails to heal VLU. Systemic therapy can be a valuable alternative in those cases who fail compression and refuse surgery as an option.[2] Besides, the compliance with compression therapy is poor among patients with VLU, particularly among older patients.[3] Oral therapy is a useful alternative in these noncompliant patients and can be used as an adjunct to the most effective modalities, compression, and local ulcer care.

PENTOXIFYLLINE

Pentoxifylline increases microcirculatory blood flow, oxygenation of ischemic tissues, increase red and white cell filterability and decrease whole blood viscosity, platelet aggregation and fibrinogen levels[4-6] (evidence Level C). Falanga *et al*.[7] demonstrated statistically significant improvement in the pentoxifylline group when compared with the placebo group, both groups receiving compression. A Cochrane collaboration study done in 2002 reported that pentoxifylline is effective as an adjuvant to compression therapy for treating VLUs[8] (evidence Level A). A well-conducted review identified 11 randomized controlled trials (RCTs) comparing pentoxifylline with placebo or no treatment. Treatment with pentoxifylline 400 mg 3 times daily improved VLU healing rates by 21% when used as adjuvant to compression or by 23% when used as solo therapy. The chief adverse effect was gastrointestinal[9] (evidence Level A). However, pentoxifylline is contraindicated in patients with severe hemorrhages, acute myocardial infarction, angina, or marked liver and kidney disease.[10]

ASPIRIN

The mechanism of action of aspirin in healing VLU is unknown. However, it is postulated that the purported reason for beneficial effects of aspirin could be inhibition of platelet activation and reduction of pain and inflammation[11,12] (evidence Level C). An RCT with methodological deficiencies in randomization, blinding and lack of mention of other treatments simultaneously and low sample size (n = 20) studied the effect of aspirin (300 mg daily for 4 months) in healing VLU. A significant reduction in ulcer size was seen in control as opposed to placebo group[13] (evidence Level C). A meta-analysis of aspirin as intervention in VLU therapy is in progress.[14] Based on current evidence, aspirin may not be effective in the treatment of VLU.

ZINC

Zinc is an essential trace metal that is necessary for some enzymes and hormones to function. Its mechanism in healing VLU is not known, but purported benefits include an antiinflammatory effect on phagocytes. It has also been noticed that zinc deficient individuals show delayed wound healing and increased risk of wound infection.[15] A Cochrane review to determine the effect of zinc sulfate orally in case of arterial, venous and mixed ulcers analyzed six RCTs consisting of 183 participants. Four out of the six trials under consideration pertained to venous ulcers. Zinc did not show any significant difference in the placebo in the healing of VLU[16] (evidence Level A).

ANTIBIOTICS

Antimicrobials

A Cochrane review analyzed five RCTs of oral systemic antimicrobial therapy involving 232 study subjects. The conclusion was that there is no routine role of systemic antibiotics in the treatment of VLU, when there is no evidence of infection[17] (evidence Level A).

Table 1: Systemic therapeutic options for VLUs

Class	Name
Alpha-benzopyrones	Coumarine
Gamma-benzopyrones	Micronized purified flavonoid fraction
	Oxerutin, rutin, rutosides
	Diosmin
Saponins	*Ruscus* extract, escin (horse chestnut extract)
Other plant extract	Maritime pine tree extract
Synthetic phlebotonics	Calcium dobesilate
Antibiotics	
Miscellaneous drugs	Pentoxifylline
	Aspirin
	Stanozolol
	Defibrotide
	Zinc

VLUs: Venous leg ulcers

LEVAMISOLE

Levamisole, a drug used for roundworm infestation, is purported to have an antibacterial action in wounds. A RCT analyzed the effect of levamisole in treating VLU enrolling 59 patients. At 20 weeks, all ulcers in the treatment group had healed as opposed to 76% healing in the placebo group[18] (evidence Level C).

Doxycycline

Doxycycline besides its antibiotic action is known to inhibit proinflammatory cytokines like tumor necrosis factor-alpha and matrix metalloproteinases, which are involved in the pathogenesis of VLU, thereby healing them.[19,20] A pilot study analyzed two dosage schedules of oral doxycycline in combination with compression in recalcitrant VLUs in 20 subjects. Doxycycline 100 mg twice a day schedule showed a median ulcer area reduction of 48% and greater suppression of ulcer fluid matrix metalloproteinase as opposed to doxycycline 20 mg/day schedule, with compression given in both arms[21] (evidence Level D). Further studies are required to evaluate the therapeutic utility of doxycycline in healing of VLU.

There is no strong evidence to support routine antibiotic use in VLU therapy at this point in time.

PHLEBOTONICS/FLAVONOIDS

Flavonoidic drugs

Flavonoids address deficiencies in microcirculatory parameters such as decreasing leucocyte adhesion, free radical formation, decreasing venous wall permeability, increasing venous tone, and protecting cells from effects of hypoxia.[22]

Micronized purified flavonoid fraction

Micronized purified flavonoid fraction (MPFF), which consists of 90% diosmin and 10% other flavonoids including hesperidin is the most widely studied among the phlebotonic drugs. It is free of any known major side-effects.[23,24] Coleridge-Smith *et al*. identified seven RCTs in which MPFF was added to compression. No benefit was seen in VLU <6 months in terms of healing. Larger ulcers of 6-12 months duration were found to benefit more from MPFF treatment. These ulcers tend to heal more slowly and hence the role of an adjunctive therapy is required more in such ulcers[25] (evidence Level A). Another meta-analysis revealed 37% increases chances of healing in VLU on treatment with MPFF[26] (evidence Level A). MPFF also has value in reducing other clinical symptoms like pain, edema and cramps as revealed in the largest study conducted in 5000 patients[27] (evidence Level B). Hence, MPFF has utility in treating venous ulcers of >6 months duration.

Hydroxyethylrutosides

Oxerutins and hydroxyethylrutosides have also demonstrated hemodynamic and Quality-of-life benefits in chronic venous insufficiency (CVI)[27,28] (evidence Level B). However, high quality evidence is lacking in case of healing VLU for oxerutins, and rutosides. The same is a case with other flavonoids such as catechins and epicatechins. A Cochrane review is in progress to analyze systematically the benefit of flavonoids alone or in combination with compression in healing VLU.[29] Pending this meta-analysis, there is no evidence for currently recommending rutosides in treating VLUs.

Phlebotonics

Phlebotonics are a heterogeneous group of medications both synthetic and plant origin, whose exact mechanism of action is unknown. The postulated benefits include the effect on macrocirculation like improving venous tone and on microcirculation by decreasing capillary hyperpermeability.[30] A Cochrane meta-analysis selected 44 RCTs involving 4413 participants - 23 of rutosides, 10 of hidrosmine and diosmin, 6 of calcium dobesilate, 2 of centella asiatica, 1 of maritime pine bark extract (pycnogenol), 1 of aminaftone, and 1 of grape seed extract. The study was to assess the efficacy in relieving clinical symptoms in CVI and not VLU. No evidence was obtained to recommend global use of phlebotonic drugs in cases of CVI. They helped in relieving edema in some studies, but this was of uncertain clinical relevance[31] (evidence Level A). Gastrointestinal disorders were the most common adverse event.

Calcium dobesilate

Is a synthetic venoactive drug thought to have antioxidant properties, reduce capillary permeability, increase venous tone and reduce inflammation.

A meta-analysis identified three RCTs, which demonstrated improvement in pain and other symptoms, more so with severe than mild disease[32] (evidence Level B). However, a meta-analysis in 2008 involving 509 patients failed to show any edema, symptoms, and quality-of-life in patients consuming calcium dobesilate in comparison with placebo[33] (evidence Level A). A trial demonstrated the increased efficacy of dobesilate with a combination with oxerutins[34] (evidence Level C). However, more evidence is required to evaluate calcium dobesilate for therapy in VLU.

Escin/horse chestnut extract

A Cochrane meta-analysis demonstrated benefits of escin in reducing symptoms and edema in CVI[35] (evidence Level A), but no evidence exists to demonstrate efficacy in healing VLU.

FIBRINOLYTIC ENHANCERS

Stanozolol

Stanozolol is an anabolic steroid with fibrinolytic activity and decreases the level of tissue plasminogen activator inhibitor.[36,37] *In vitro* studies have demonstrated procollagenase synthesis enhancement in fibroblasts.[38] Multiple studies have demonstrated the efficacy of clearing of fibrosis on therapy of lipodermatosclerosis by stanozolol in combination with the compression[39,40] (evidence Level B). However, multiple studies have demonstrated a lack of effect on healing venous ulcers located within the lipodermatosclerotic patches.[41,42] The reason of same is not known. Evidence does not support the use of stanozolol routinely in the treatment of VLU.

Defibrotide

Defibrotide is an antithrombotic and profibrinolytic drug. In a crossover trial involving 32 patients defibrotide 400 mg tid along with compression was compared with placebo and found to be more efficacious in healing VLU[43] (evidence Level D).

MESOGLYCANS

Mesoglycans are glycosaminoglycans extracted from porcine intestine and is composed of heparan sulfate, dermatan sulfate, and chondroitin sulfate. Its exact mechanism of action is not known, but it has a profibrinolytic action, microrheologic, and macrorheologic benefits and has been reported to be useful in treating venous disorders.[44] It inhibits neutrophil adhesion and activation, and enhancement in the process of wound healing.[45] One multicenter RCT compared mesoglycan IM/oral and compression with placebo and compression therapy and demonstrated clinically significant benefit in time to healing. However, the study was compromised by baseline differences between groups and nonstandardization of compression therapy[46] (evidence Level C).

CILOSTAZOL

Cilostazole is a phosphodiesterase-3 inhibitor and is a vasodilator and platelet inhibitor by increasing the levels of protein kinase A[47] and has been used in the treatment of intermittent claudication. There is no good quality evidence currently for recommending cilostazol in routine therapy of VLU.

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