

**Review Article****Current understanding on venous leg ulcer**U Alok^{1*}, P Bhardwaj², A Singh³, JJ Cherian⁴¹TATA Consultancies Services, Regulatory Medical Writing, Wellspring, Vikhroli, Mumbai, Maharashtra, India²Quintiles Research India Pvt. Ltd, Bangalore, Karnataka, India³Bharati Vidyapeeth University Medical College, Pune, Maharashtra, India⁴Government Medical College, Department of Pharmacology, Thiruvananthapuram, India**ARTICLE INFO:****Article history:**

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ABSTRACT

Venous leg ulcer (VLU) or stasis ulcer is a relatively common, chronic and recurring problem. Besides being costly to the health-care system, it significantly impairs the quality of life of the patients. Nearly 1% of adults and 3.6% of older patients are reported to suffer from this chronic condition. Chronic venous insufficiency is considered to be the predominant cause of VLU. The most recent theories associate the pathogenesis of venous ulcer with microcirculatory abnormalities and generation of an inflammatory response. The pharmacological treatment for VLU is based on the pathogenesis and often includes diosmin, pentoxifylline, diuretics as well as antibiotics and the non-pharmacological treatment like compression and skin grafting. VLU has a high rate of recurrence and requires self-care to avoid relapse. Treatment of VLU should always focus for complete treatment, and improve quality of life for patients along with minimum relapse. In recent years novel therapeutic approaches for venous ulcers have offered valuable tools for the management of patients with this disorder.

Introduction

Venous leg ulcers (VLU) or stasis ulcers are a chronic and recurring problem that is very taxing to the health-care system and significantly impair the quality of life of those who suffer from it. The incidence of chronic venous insufficiency is approximately 5.9% and the prevalence of venous ulcers is around 1% in the Western world [1]. The prevalence of VLU increases with age from 4% to 5% in elderly patient of ≥ 80 years old [2,3]. Many studies suggest a higher prevalence of venous leg ulcers in women, but this disparity decreases with age [4].

VLU account for 60-80% of lower leg ulcers [5]. Studies report that an average venous ulcer requires as much as 6 to 12 months to heal completely and 70% of which could recur within 5 years of closure [6]. Chronic venous insufficiency is the most common cause of leg ulcers.

Etiology

Chronic venous insufficiency and related venous ulcers are predominantly caused by prolonged venous hypertension. This

may occur due to one or more of the following reasons [7]. (1) Obstruction (venous outflow), for example secondary to deep vein thrombosis (DVT) or trauma (including previous lower limb fractures and surgery), pelvic mass, pregnancy, ascites, or obesity. (2) Venous reflux / Valvular incompetence, for example damage to valves via thrombophlebitis, as a consequence of ageing or congenital venous abnormalities. (3) Muscle pump failure, for example immobility related to ageing and co-morbid disease, paralysis or sedentary lifestyle.

Pathophysiology

Various theories have been put forward to explain the pathophysiology of venous ulcers, among them predominant theories are fibrin cuff and white blood cell trapping theory. According to the fibrin cuff theory, increased venous pressure causes leakage of macromolecules from plasma into perivascular space. This initiates the conversion of fibrinogen to fibrin and acts as a barrier to diffusion of oxygen and nutrients [6]. A recent hypothesis proposed that normal venous

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circulation in the extremities is regulated by unidirectional valves that facilitate blood flow from capillary beds to the superficial system and finally to the deep venous system. When primary valvular dysfunction (the valves leading from the superficial to the deep venous system stop functioning properly), occurs it leads to localized ambulatory venous hypertension in the superficial veins [8,9].

Theory of white blood cell trapping suggests that the red blood cells and macromolecules which include fibrinogen and alpha-2 macroglobulins, escape into dermis from circulation, due to venous hypertension. Since they cannot re-enter the circulation, they undergo degradation and the degraded products act as potent chemo-attractants. These inflammatory mediators attract leucocytes, and the resultant leukocyte's migration and activation results in cytokine/growth factor release, soft tissue destruction, remodeling, dermal fibrosis and eventually ulceration [10]. Prolongation of this phenomenon induces transforming growth factor beta-1 (TGF beta-1), a cytokine released by macrophages and mast cells mediating dermal fibrosis in patient with severe ambulatory venous hypertension. TGF beta-1 binds to dermal fibroblast and regulates tissue remodeling by synthesis of collagen, regulation of metalloproteinase, differentiation of myofibroblast and extracellular matrix contraction [11].

Recent research has shown that fibroblasts from the edges of non-healing venous ulcers are unresponsive to TGF-beta-1, which may contribute to the overall failure in wound healing [12].

Clinical feature

VLU's are usually distributed in the calf, gaiter and foot region of the leg with distribution percentages of 5%, 87% and 8% respectively (Figure 1) [13]. The size of the ulcer is usually large with irregular or ragged borders. Wound bed appears to be bright red with shallow depth (Table 1). The patient often gives history of pain, unpleasant odor, exudation, spontaneous bleeding and alteration of lifestyle. Clinical signs of venous disease include varicosities, hyper-pigmentation (due to hemosiderin staining), atrophie blanche, dermatitis, edema and lipodermatosclerosis (woody texture to the skin) [14]. Leg ulcers are often classified by their predominant etiology into venous and arterial leg ulcers. Venous and arterial leg ulcers are predominant followed by diabetic related ulcers. Comparison of clinical features of venous and arterial leg ulcers are summarized in table 1.

Table 1: Clinical feature of venous and arterial leg ulcer

Clinical feature	Venous	Arterial
Location	calf, goiter, foot region and medial aspect	usually over toes, foot and ankle
Depth	Shallow	deep
Wound Edges	irregular ragged bordered	punched out
Wound Bed	bright red, fibrinous, loose slough or necrotic	often covered with varying degree of slough and necrotic tissue
Exudates	copious, sometimes dripping, serous or bloody	usually low
Pain	mild to severe, decreased with elevation or compression	pain, even without infection
Pulses	readily palpable one edema is reduced	reduced or absent
Associated features	venous eczema, lipodermatosclerosis, atrophie blanche, hemosiderosis	trophic changes; gangrene may be present

Diagnosis

Proper physical examinations as well as diagnostic investigation are crucial in deciding the right treatment option. Both limbs should be assessed for edema, temperature, and absence/loss of hair. Cold, clammy limb and loss of hair over the foot may indicate arterial insufficiency. Doppler measurement of the pressure at the ankle (dorsalis pedis or

posterior tibial artery) in addition to the brachial artery is performed to determine Ankle Brachial Pressure Index (ABPI).

ABPI = (Ankle Systolic Pressure / Brachial Systolic Pressure). Both the brachial and the ankle systolic pressures are obtained by using a portable Doppler. In a healthy vascular system, the ankle brachial pressure index is 0.9 to 1.2. An ABPI of 0.80-0.9 indicates mild ischemia which may be the consequence of

an inflow disease; 0.50-0.79 indicates moderate ischemia; 0.35-0.49 indicates moderately severe ischemia; 0.20-0.34 indicates severe ischemia and < 0.20 indicates critical ischemia [14].

Doppler ultrasonography is a method used to confirm venous reflux, but it cannot differentiate between superficial and deep venous insufficiency. Photoplethysmography (PPG), on other hand has an advantage of distinguishing between superficial and deep vein incompetence by measuring the extent of light absorption [15]. Duplex Doppler ultrasonography, a combination of ultrasonic scanning and pulsed Doppler flow examination, enables anatomical and functional assessment of the venous system but is not widely available [8].

The ulcer should be swabbed for microbiological testing, as more than 80% of leg ulcers may be colonized with bacteria [16,17,18]. The most common micro-organisms infecting the wound are *Pseudomonas aeruginosa*, *Staphylococcus aureus* and Hemolytic streptococci, which can slow the ulcer healing process [19]. Musculoskeletal examination like goniometry (extent of joint movement) is sometimes warranted to assess loss of mobility at the ankle joint, loss of calf muscle pump function and loss of joint mobility of the toes due to VLU [20]. Complete blood count and random blood sugar should also be monitored before starting the treatment regimen.



Figure 1: Chronic ulcer on the medial malleolus

Treatment approaches

Non pharmacological

Non pharmacological approach includes appropriate dressing and graduated compression therapy. Current standard clinical approach to therapy includes lower limb compression along with leg elevation and debridement, which heals 40 to 60 percent of venous leg ulcers. In a 2009 Cochrane review, evaluated a total of 39 randomized controlled trials and concluded that there was reasonable evidence to suggest limb compression healed venous ulcers more rapidly [21]. Debridement is also an important measure in the treatment of VLU [22]. Debridement of necrotic debris should be done as it encourages the growth of granulation tissue. However, the mainstay treatment for venous stasis ulcers is compression. Compression can be provided by dressings: single or multilayered bandaging, graduated compression stockings, or Velcro-strap devices. Compression materials used may be elastic or inelastic, like bandage wraps, Unna's boot, elastic stockings and mechanical devices. Sustained graduated compression overcomes the effects of venous hypertension by reducing venous stasis and preventing tissue edema [23]. European standard compression hosiery proposes four classes of compression at the ankle: light compression (18.4–

21.1 mm Hg/2.5–2.8 kPa); medium (25.2–32.3 mm Hg/3.3–4.3 kPa); strong (36.5–46.6 mm Hg/4.9–6.2 kPa); and very strong (>59 mm Hg/ >7.9 kPa). Light compression hosiery is indicated for treating mild varicose veins; medium compression for pronounced varicosity with edema and strong compression for late complications of constitutional or post-thrombotic venous insufficiency, atrophie blanche, dermatosclerosis [24]. However the most effective level of compression to overcome venous hypertension has been determined to be around 40 mm Hg at the ankle [21]. The recent Cochrane review provides the most complete overview on randomized controlled compression-trials in venous leg ulcers and concluded that compression clearly increases the rate of healing as compared to no compression [25].

Treatment by multilayer elastic compression is presently an effective form for the treatment of venous ulcer. The pressure sustained in this type of compression is between 40 and 45 mmHg at the ankle and 17 mmHg below the knee. These multilayer compression materials have first layer of woolen fabric applied as spiral, which absorbs exudates and redistributes pressure around the ankle. The second layer is a compression elastic bandage, and the top layer is an adhesive bandage that adequately sustains all layers [26]. This compression can last in the place for seven days with

sustained pressure, trauma protection, for wounds with exudates. The multilayer system is more effective than the traditional ones [27]. High compression is more effective than low compression, but the differences in effectiveness of the many types of high compression are not yet clear [28]. Choice of dressings may change during the course of therapy concomitant with the changing nature of the wound base and exudate.

The effect of surgery and compression on healing and recurrence (ESCHAR) trial randomized 500 limbs to high ligation and stripping of the saphenous veins (saphenectomy) in addition to compression versus compression alone [29,30]. Initial results of ulcer healing were similar in both the groups (93% and 89%, respectively) but ulcer recurrence at 4 years (24% vs. 52%) was significantly better in the saphenectomy group. The study suggested that the correction of saphenous reflux prevented recurrence. In a recent study, considering compression as a form of medical saphenectomy, it was suggested that compression stockings mechanically compress the saphenous and deep veins (with higher pressures), thereby abolishing reflux [31].

Ideally, compression should be accompanied by complete bed rest and leg elevation to relieve edema; however, this is not always practical [15]. Leg elevation helps in reducing edema and enhances flow in the microcirculation, reducing trapping, sequestration, and activation of white cells [21].

If conservative treatment by leg compression is unsuccessful, surgical intervention like skin grafting is required [32]. Grafting may be pinch graft which is advisable in patients with multiple medical problems, and can be performed on an outpatient basis and in primary care facilities [33]. Split thickness skin graft is used for large ulcers. These grafts need a large donor site as these may contract after harvesting and can be slow to heal, causing a lot of pain. Major disadvantage of large skin graft is treatment failure because of the build-up of exudates underneath the graft. This failure is best avoided by the use of a meshed graft [34]. Other adjunct treatment for venous ulcers includes electrical stimulation, negative pressure therapy, hyperbaric oxygen therapy, ultrasound, and low-intensity laser therapy. However, the effectiveness of this adjunct treatment in amelioration of VLU is uncertain [35].

Pharmacological

Antibiotics, diuretics pentoxifylline, aspirin and diosmin, are among the drugs, used in the treatment of VLU (Table 2). Antibiotics have little effect on ulcer healing and are needed if there is a clinical infection with surrounding periulcer erythema, swelling, cellulitis, purulence, tenderness and pain, and sometimes fever and malaise. In cases where infection results in septicemia, intravenous therapy of antibiotic is necessary [36]. Ulcers of less than 1 month duration usually are colonized by Gram-positive organisms (*Staphylococcus aureus*, and Group-A streptococcus). Cephalexin is an ideal choice of antibiotic, although cloxacillin is often used as well but does not adequately cover streptococcus species. Gram-

negative and anaerobic organisms may co-exist in ulcers of longer duration, and a broad spectrum of antibacterial coverage should be considered.

Diuretics are among the most commonly used drugs in the treatment of edema associated with venous ulceration. Diuretics may help mobilize fluid in conjunction with aggressive compression therapy, but they are ineffective if given alone for edema control [37].

Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates PKA, inhibits TNF and leukotrienes synthesis [38,39], and reduces inflammation. In a placebo controlled, double blind, randomized study out of 80 patients; 88% healed by 12 months on pentoxifylline compared to 44% on placebo [40]. Aspirin has also been evaluated for the treatment of VLU in a small randomized clinical trial. In the study aspirin was compared with placebo and was found that 38% of ulcers healed with aspirin in comparison to 0% by placebo. However the validity of the study has been challenged by the weak methodology of the conducted trial [41].

Phlebotonic, which are flavonoid are either derived from plant source or prepared synthetically, like diosmin (derived from the flavonoid, hesperidins, found in citrus rinds) have been evaluated for their healing effect on VLU. The mechanism of action is not well established yet, but they seem to act on microcirculation, improve venous tonus, and decrease capillary hyper permeability [42]. Diosmin acts by reducing pain sensation, swelling, tension, and heaviness in the legs which are associated with chronic venous disease [43]. In a crossover study of the topical polymeric starch iodophore, (cadexomer iodine), patient's condition improved with the treatment. Ulcers treated with cadexomer iodine showed trends toward less pain, exudation, pus, and debris, and a more rapid development of granulation tissue [44]. One multicentric RCT (Randomized Controlled Trial) compared mesoglycan (30 mg administered as daily intramuscular injection for three weeks followed by 100 mg orally daily) with placebo in 183 patients with venous ulcer receiving compression therapy. The primary end point was time to healing of the target ulcer. At 24 weeks the relative risk of healing was 1.48 (95% CI 1.05 to 2.09) in favour of mesoglycan. Compared with other studies, the ulcers were of relatively short duration and the healing rate high. There were also differences at baseline between the groups and the use of compression bandaging was not standardized [45]. There is insufficient evidence to base a recommendation for mesoglycan in chronic VLU.

Herbal therapy is also becoming increasingly popular among patients and physicians for treating VLU. An open, randomized controlled trial established the efficacy of new DermpalantG (contains dry water extract of *Allii bulbis*, dry ethanol extract of *Hyperici herba* and oily extract of *Calendulae flos*) herbal therapy in patients with non-infected venous leg ulcerations. The result of the study showed an accelerated process of epithelization and healing of certain venous ulcers without any observed adverse effects during the study and with good skin tolerance [14]. Herbal-based ointment Herbadermal® in a prospective non-randomized

pilot study showed 99.1% epithelization of ulcer after 7 weeks of treatment [31].

Several other advances are also under study and are offering promising results in the treatment of venous ulcers. Topical

application of various growth factors [e.g., platelet-derived growth factor (PDGF), combination of platelet-derived wound-healing factors (PDWHF)], have been shown to accelerate healing of chronic non-healing ulcers [46,47,48].

Table 2: Treatment options for VLU

Non Pharmacological	compression, debridement skin grafting
Pharmacological	analgesics, antibiotics, diuretics, topical antimicrobials, local anesthetic, topical corticosteroids, pentoxifylline, phlebotonics growth factors (PDGF, PDWHF)
Patient's education and self-care	follow up care, leg elevation, smoking cessation

Patients' education and self-care

Patient compliance and education is essential for the successful treatment of VLUs. Despite healing of a venous ulcer; each patient should receive sufficient follow-up care. The patient should be instructed about proper skin care and the importance of leg elevation and also to avoid prolonged standing. Appropriate rest is important for ulcer healing, since it decreases the effects of venous hypertension. During rest, the limb should be raised above the level of the heart, for at least 30 minutes, three or four times a day [49]. Short walks, three or four times a day, should be encouraged. Besides, patients should be encouraged to maintain their weight in a range considered normal, and to cease smoking [50]. Besides this, an evident educational program should be encouraged for primary care providers about their role in guiding the patient about the necessity for achieving an accurate diagnosis.

Clinical studies

Several clinical trials are currently underway to reveal new potential treatments and directions of the management of VLU's. An open label, phase I trial of Protein Kinase C (cPKC) based formulation (HO/03/03) has shown promising results in advancing the healing rate of venous ulcer. A human amniotic membrane allograft (EpiFix), in an open randomized controlled trial has shown to be effective in healing wounds. Amniotic membrane is rich in growth factors which are essential elements in wound healing by inhibiting inflammation and infection and also by promoting proliferation and differentiation of keratinocytes [51,52].

A phase II study to investigate the efficacy, safety and tolerability of topical treatment with Nexagon is presently recruiting subjects. The preclinical evidence with Nexagon as a wound healing promoting agent was promising. Nexagon acts by inhibiting a protein named Connexin 43 found in the gap junction of epidermal cells. Evidence is provided by a study which suggested the up-regulation of Connexin 43 in ulcer wound in comparison to intact skin [53]. By down-

regulation of this protein in the ulcer site, the extent of migration of fibroblasts increases, thereby potentiating wound healing. A phase I clinical study of topical Fibroblast Growth Factor 1 for chronic ulcers however failed to elucidate the efficacy of the intervention in humans, but a certain wound closure action was reported in one of a preclinical study [54]. Venous ulcer fibroblasts demonstrate a lack of viable TGF-receptor complexes, which may contribute to the chronicity of these wounds [21]. An elaborate study is needed to elucidate the wound healing potential of fibroblast growth factor 1. CureXcell, a product containing activated allogenic white blood cells (monocytes, macrophages, neutrophils, and lymphocytes from healthy donors) recently proved to be effective in treating ulcer which is difficult to heal. This study was a prospective, cohort trial that showed monocyte and macrophage activation results in enhanced phagocytosis and secretion of cytokines that promote healing [55].

Discussion

The effective amelioration of the symptoms of VLU using pharmacotherapy and therefore avoiding the adverse events of surgery is an attractive and desirable goal. The lack of universally accepted and effective pharmacotherapy for venous disease highlights the multifactorial nature of the symptoms suffered by these patients. Factors like obesity, calf muscle pump function, co-morbidity (particularly cardiac disease) and other medication may all contribute to the symptoms thought to originate from venous incompetence. Clearly a multidisciplinary approach must be considered for their clinical management.

Current research focuses on the role of superficial venous surgery and the use of cultured skin allografts. Optimization in level of compression for healing should be explored. Variety of cell derived soluble factors, proteolytic enzymes (proteases) and cytokines (growth, regulatory, and chemotactic factors); are thought to direct wound healing processes and are current targets for specific treatment [56]. Leg ulcers may reoccur with the same frequency of ulceration. Recurrence rates of venous ulcers after treatment are reported to be high

[57](Barranco 1974). Once the leg ulcer is healed, careful skin care, continuous vigilance, and strict use of compression hosiery must be emphasized. Ultimately, the treatment focus should move from treating active ulcers to prevention; which would undoubtedly be cheaper than their cure and would also improve quality of life for patients with VLU.

Conflict of interest statement

We declare that we have no conflict of interest.

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