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Review Article

# Are Drugs Indicated and Efficient in the Management of Venous Ulcer?

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## Abstract

The pathophysiology of chronic venous disease is characterized by venous hypertension, which triggers endothelial dysfunction and inflammation leading to microcirculatory and tissue damage, to varicose veins and venous ulcers. These last are the most severe expression of Chronic Venous Disease (CVD) and are due to complete failure of the compensatory pathophysiological mechanism of the microcirculatory system.

## Introduction

The therapeutic strategies in the treatment of CVD include physical methods, such as elevation of the legs, compression therapy with bandages or elastic stockings, open surgical or endovascular correction of superficial or perforating vein incompetence and drug treatment. With our present understanding of the pathophysiological events in CVD, it has become clear that there are both macrocirculatory and microcirculatory alterations that need to be targeted by treatment. Compression therapy and surgical procedures are targeted mainly towards the macrocirculation. Drug treatment, thanks to its comprehensive mode of action, addresses both the macro- and the microcirculation at the same time and a variety of drugs has been used in the management of CVD and venous ulcers [1].

These include Venoactive Drugs (VADs), diuretics, Acetylsalicylic Acid (ASA), topical and systemic antibiotics, topical corticosteroids, horse chestnut seed extract, topical antiseptics, silver sulfadiazine, anabolic steroids, hydroxyethylrutoside, enzyme debriding agents, growth factors and others [2].

Treatment to inhibit inflammation may offer the greatest opportunity to prevent disease-related complications. Currently available VADs can attenuate various features of the inflammatory cascade, particularly the leucocyte-endothelium interactions that are important in all aspects of the CVD [3].

Micronized Purified Flavonoid Fraction (MPFF) is a most representative VAD that is composed of a semi synthetic micronized preparation of the γ-benzopyrone family consisting of 90% diosmine and 10% hesperidine [4,5]. It has demonstrated phlebotonic activities, lymphokinetic abilities and modulation of inflammatory mediators and hemorrheogical parameters in preclinical studies, as it has been extensively reviewed [2].

In animal studies, MPFF has been shown to suppress post-ischemic leukocyte/endothelial cell interactions that are similar to the processes that are thought to lead to venous ulceration [3,4].However, the final evidence that this drug's effect has clinical implications comes from the ability of the drug to facilitate venous ulcer healing in patients.

In a multicenter double-blind randomized, placebo-controlled study [5], the efficacy of MPFF was demonstrated in improving healing of venous leg ulcers. Patients (n=107) suffering from active venous ulcers were included in this study. They were divided into two groups that received MPFF 500 mg, bd, or placebo in combination with standard therapy (both local therapy and conventional compression therapy). After 2 months of treatment, the percentage of complete ulcer healing in the MPFF group was significantly higher than that of the placebo group: 31.8% of venous ulcers healed in the MPFF group compared with 12.8% in the placebo group. The MPFF combined with standard therapy healed three times more venous leg ulcers than standard therapy with placebo, and in a shorter time.

In the study by Glinski et al [6]. 140 patients affected by venous leg ulcers were enrolled to receive standard compressive therapy plus external treatment alone, or MPFF 500 mg bd daily in addition to the above treatment for 24 weeks. Ulcers with a diameter less than 3 cm were cured in 71% of the MPFF group and 50% of the standard therapy group. When the ulcer's diameter was between 3 and 6 cm, they were cured in 60% and 32% ($P < 0.05$) in the MPFF group and the control group, respectively. As a whole, the group which received MPFF presented a significantly higher ulcer healing rate than the other group (46.5% *vs.* 27.5%, $p < 0.05$).

The beneficial effect of MPFF has also been demonstrated, in terms of the percentage reduction in the ulcer area. The reduction in size was most prominent during the first 2 months of treatment, independent of initial ulcer size. This was also observed in patients with ulcers more than 6 cm in diameter, in whom about a 65% reduction was found after 24 weeks of MPFF treatment [7].

These studies showed that treatment with MPFF 500 mg bd, in addition to conventional compression therapy, is of benefit in patients with venous leg ulcers, as it accelerates complete healing. An explanation for the ability to speed ulcer healing comes from recent evidence that MPFF 500 mg bd treatment for 60 days decreases the immunoglobulin-like endothelial markers Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), involved in the adhesion of neutrophils and monocytes to the endothelium. The MPFF decreases leukocyte trapping and activation which may explain its anti-inflammatory effects [7-10].

Although several pharmacological and surgical strategies are being utilized in the management of varicose veins and CVD with variable success and recurrence rate, inhibition of Matrix Metalloproteinases




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(MMPs) through glycosaminoglycans may represent a novel therapeutic intervention to limit the progression of varicose vein to CVD and leg ulceration, suggesting possible opportunity to prevent future morbidity and enhancing clinical benefits and quality of life [11-14].

Ultimately, the focus of CVD therapy should move from treating active ulcers to avoid CVD progression and ulceration in an effort to reduce the socio economic cost incurred by this disease [9]. The beneficial effects on venous pressure and the signs and symptoms of CVD indicate that glycosaminoglycans are a useful treatment option for the prevention of venous ulcers, but this indication should be formally investigated [15]. The anti-inflammatory activity of glycosaminoglycans and their effects on preserving and restoring endothelial function and restoring a good balance between MMPs and their tissue inhibitors suggest that this therapy may reduce or prevent the pathophysiologic changes leading to the development and progression of venous ulcers [10,15].

Pentoxifylline, which is indicated in the management of peripheral arterial disease, has also been used in the management of venous leg ulcers. In a review of 12 clinical trials involving 864 patients, Pentoxifylline improved venous ulcer healing on its own and when used in combination with compression compared with placebo [16].

Also prostanoids, specific drugs for the treatment of critical limb ischemia, have been used in the extensive chronic venous ulcers due mainly to post-thrombotic syndrome [1-16].

The use of diuretics should be restricted to a short time in patients with severe edema. A common but unproven practice is to use a mild diuretic, such as hydrochlorothiazide, for 7 days prior to fitting compression stockings in order to achieve the most accurate fit [16]. This is only useful in patients with edema [16].

The antiplatelet agent ASA may accelerate the healing of chronic venous ulcers. In a double-blind randomized clinical trial involving 20 patients, 300 mg of enteric coated ASA od significantly improved the number of healed ulcers at 4 months compared with placebo (38 *vs.* 0%, respectively), and increased the number who achieved a significant reduction in ulcer size (52 *vs.* 26%, respectively [1]. All patients in this study were also treated with compression bandages.

Most venous ulcers are heavily contaminated with bacteria including *Staphylococcus*, *Streptococcus*, *Escherichia coli*, *Proteus* and *Pseudomonas*. Nevertheless, the routine of administration of topical or systemic antibiotics has not resulted in reduced bacterial colonization or improved healing rates; furthermore, this approach may be complicated by an increased incidence of contact dermatitis and the emergence of resistant organisms [1,2]. Topical antibiotics should probably be avoided completely. Systemic antibiotics should be reserved for patients who have the signs and symptoms suggesting significant infection as fever, increased pain, increasing erythema of the surrounding skin, lymphangitis and rapid increase in the size of the ulcer [1,2].

Routine swabbing of leg ulcers is unnecessary in the absence of the above signs of infection [1,2]. If infection is suspected clinically, the ulcer should be cultured and antibiotic selection should be based upon the results. Cultures can be obtained in one of two ways: by irrigating the ulcer, then performing a 2 to 3 mm punch biopsy and sending the tissue for culture; or by injecting 2 to 3 ml of sterile saline into the dermis, then quickly withdrawing the fluid back into the syringe and sending for culture [1,2,16].

Empiric treatment pending culture results should target Gram positive and negative organisms, including *Pseudomonas* [1,2]. Empiric antibiotic choices may include dicloxacillin, cephalexin, or ciprofloxacin, depending upon the degree of suspicion for Gram negative organisms.

Uncomplicated stasis dermatitis usually responds to the topical application of steroids or emollients [1,2]. Failure to respond suggests the possibility of contact dermatitis and the need for patch testing. Horse Chestnut seed Extract (HCE) stimulates the release of F series prostaglandins, such as Prostaglandin $F_{2\alpha}$ (PGF2-alpha) which induces venoconstriction, and decreases the permeability of vessel walls to low molecular proteins, water and electrolytes [1]. This oral compound is used in Europe to treat hemorrhoids, varicose veins, cyclical edema, and tired, heavy legs [1,2].

The HCE at a dose of 50 mg of escin (the active compound) bd was superior to placebo and equivalent to compression stockings for reducing leg volume and edema in patients with CVD [1]. These positive results were confirmed in a meta-analysis which found that 50 to 75 mg of escin orally bd not only improved symptoms compared with placebo, but also provided a comparable degree of benefit with compression and other medications [2,16].

Topically applied antiseptics, including hydrogen peroxide, povidone iodine, acetic acid and sodium hypochlorite have been shown in vitro and in animal studies to have cellular toxicities that exceed their bactericidal activities [1,2] All except hydrogen peroxide impair wound epithelialization and are not recommended [1,2].

Silver sulfadiazine has a long tradition of use in the treatment of cutaneous wounds, including burns, partial thickness wounds, and skin graft donor sites [16]. This topically applied drug inhibits the growth in vitro of nearly all pathogenic bacteria and fungi, including some species resistant to sulfonamides. The mechanism by which it reduces microbial colonization of wounds is via the slow release of silver in concentrations that are selectively toxic to bacteria [1]. A small amount of silver is absorbed systemically, and sulfadiazine blood levels can reach therapeutic levels if the wound surface is large [16].

Randomized trials that have examined the use of silver sulfadiazine in the treatment of venous ulcers have had mixed results. One study, for example, compared silver sulfadiazine to a tripeptide copper complex and inert petrolatum; silver sulfadiazine was significantly more effective in promoting ulcer healing (21% vs. 3%) [1,2,12]. Adverse effects associated with the use of silver sulfadiazine include induction of bacterial resistance and contact dermatitis [1,12].

Stanazole, an anabolic steroid, stimulates blood fibrinolysis and has been tested in a randomized placebo controlled trial for the treatment of the more advanced skin changes associated with lipodermatosclerosis (a fibrosing panniculitis of the subcutaneous tissue) [1,2,12].

Hydroxyethylrutoside (HR) is a standard mixture of semisynthetic

flavonoids that act mainly upon the endothelium of the microvessels to reduce permeability and edema [12]. Related to these changes is an increase in the partial pressure of oxygen in the leg veins and the transcutaneous oxygen tension of patients with Chronic Venous Insufficiency (CVI). The HR has been used in Europe for more than 30 years to treat various types of dependent edema.

The HR decreases leg volume in patients with CVI; in one study it was found to be superior to HCE, with 75% of patients achieving a response [16].

The accumulation of pus and fibrin may delay the healing of chronic ulcers by preventing granulation and epithelialization. Several enzyme debriding agents are available, including krill enzymes (from antarctic shrimp), which consist of natural endopeptidases and exopeptidases capable of breaking down proteinaceous substances to soluble free amino acids. These agents have been shown in some reports to effectively debride ulcers, although compelling evidence for their use in the treatment of venous ulcers is lacking [16].

Several growth factors play a role in wound healing, including platelet derived growth factor, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors [1,2,16]. A few well controlled randomized clinical trials have assessed the use of growth factors in the healing of a variety of chronic ulcers and found conflicting results [1,2]. In venous ulcers specifically, growth factors have not been shown to enhance healing rates.

In conclusion, leg elevation and compression therapy are the mainstay of treatment in most patients with CVD and venous ulceration. Drug therapy may be considered in the following circumstances: diuretic use is restricted to a short time in patients with severe edema; ASA and other antiplatelet drugs may accelerate the healing of chronic venous ulcers; it is recommended in patients with ulcers who do not have a contraindication to its use; systemic antibiotics should be used only in patients who have signs and symptoms of ulcer infection; uncomplicated stasis dermatitis usually responds to the topical application of corticosteroids or emollients. Horse chestnut seed extract reduces leg volume and edema in patients with CVD; it may be used in patients who refuse to wear compression stockings, or for those in whom compression is contraindicated (e.g. occlusive arterial disease). The dose is 300 mg (50 mg of escin) bd. Hydroxyethylrutoside is an alternative. Topical antiseptics, antibiotics, debriding enzymes, growth factors, and silver sulfadiazine are not recommended.

The main cornerstone of treatment of CVD is represented by the venoactive drugs such as MPFF and glycosaminoglycans; for this drug it is possible to propose a strong recommendation for its use in the therapy of advanced stages of CVD, examining the different guidelines based on evidence [1,2].

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