

Medical Treatment of Chronic Venous
Disease

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Abstract

Chronic Venous Disease (CVD) of the lower extremities is a complicated disorder that affects the productivity and well-being of millions of people worldwide. Management requires careful differential diagnosis and a systematic long-term multidisciplinary care effort directed toward realistic goals within the context of the patient's lifestyle.

Patients suffering from any class of the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification of Chronic Venous Disease (CVD) may be symptomatic (C0s-C6s). Leg heaviness, discomfort, itching, cramps, pain, paresthesia and oedema (C3) are the most frequent manifestations of CVD and a major reason for medical consultation. The standard treatments for venous disease of the lower limb include compression bandaging and stocking as well as surgical removal of varicose veins. Drugs for the venous system were initially called phlebotonics as they were believed to act on venous tone. They are still largely used in the symptomatic treatment of CVD and to make patients more comfortable.

Phlebotropic drugs, in their modern form, are aimed at a wide range of processes. They are naturally occurring, semi-natural or synthetic substances, some of them combining two or more active principles to improve the efficacy.

Most of these belong to the flavonoid family (such as Diosmine, Esperidine, Troxerutine, Oxerutine, etc) and others are capillary protecting substances as Escine, Centella Asiatica, and Bilberry Anthocyanosides. Flavonoid drugs have been widely used in the management of the symptom of venous disease for many years and have recently been studied in some detail to assess their effects on the microcirculation.

Phlebotropic drugs are widely prescribed and marketed in Italy, France, Germany and other parts of Europe.

Their mechanisms of action vary, but their main property is activation of venous and lymphatic return. The effects of Phlebotropic drugs on physiological parameters such as venous tone, venous hemodynamic, capillary permeability and lymphatic drainage have been studied by many well-conducted randomized, double-blind clinical trials. In particular, Phlebotropic drugs participate in the hemodynamic re-equilibrium of the microvascular system consisting in reducing capillary permeability by increasing its resistance with the consequent reduction of interstitial fluid.

A series of drugs have been recently introduced for the treatment of severe CVD (CEAP 4/5/6), as co-adjuvant. They are antithrombotic drugs (Sulodexide, Mesoglycan, Heparan Sulfate, Defibrotide) and vasodilators (pentoxifyllin and prostaglandin E1) for their specific action on endothelial alterations and blood flow patterns, and on micro thrombi and their oxygen barrier effect.

Introduction

Chronic Venous Disease (CVD) of the lower limbs is characterized by symptoms or signs produced by venous hypertension as a result of structural or functional abnormalities of veins [1]. The most frequent causes of CVD are primary abnormalities of the venous wall and the valves and secondary changes due to previous venous thrombosis that can lead to reflux, obstruction, or both. Congenital malformations are rare causes of CVD [1].

CVD has a considerable socio-economic impact in Western countries due to its high prevalence, cost of investigations and treatment and loss of working days [2,3]; it is also an important cause of discomfort and inability to work.

The Framingham study found an annual incidence of 2.6% among women and 1.9% among men [4] of CVD. Varicose veins are present in 25% to 33% of female and 10% to 20% of male adults [5,6]. Venous ulcers occur in 0.3% of the adult population in Western countries [7-12].

An international classification system is mandatory to obtain a basic tool for uniform diagnosis, treatment and meaningful scientific communication on CVD. The consensus report of the American Venous Forum in 1994 presented the CEAP classification, which addressed the clinical, etiological, anatomical, and pathophysiological mechanisms of CVD with the need for objective testing (Table 1) [13].

The clinical classification was sub classified according to whether the patient was asymptomatic or symptomatic. The etiological classification recognized congenital, primary and secondary causes of venous dysfunction. The anatomical classification considered the site and extent of

involvement of the superficial, deep and perforating veins, and the pathophysiological classification took into account the site and extent of reflux, obstruction or both.

CEAP has been promulgated around the world and it has been published in 23 separate journals and books in 8 languages and in 5 continents [14,15]. Although the CEAP classification provides a system for documentation of the severity of CVD, it is often necessary to evaluate individual symptoms, signs or physiological parameters, clinical outcome, and quality of life also for the best choice for treatment.

Clinical manifestations of CVD differ, depending on the stage of the illness, and can include symptoms as aching, heaviness, leg-tiredness, cramps, itching, sensations of burning, swelling, the restless leg syndrome, dilatation or prominence of superficial veins and skin changes, and signs as telangiectasia, reticular or varicose veins, oedema, and skin changes such as pigmentation, lipodermatosclerosis, eczema and ulceration [15].

Although surgery, sclerotherapy, and mechanical compression are generally the preferred treatments, pharmacologic treatments are often used because they are easy to administer and there is poor compliance with compressive treatments [16,17].

Drugs Therapy

In many countries, drugs remain widely used as adjunctive treatments in patients with vein problems [18,19].

Most drugs used are plant extracts but they can be chemically treated to improve bioavailability, for example by micronization, which increases the gastrointestinal absorption of certain flavonoids. Synthetic agents are in the minority. Pharmacotherapy does not prevent or regress varicose veins but provides effective and objective relief for many patients at various stage of CVD [20].

In particular, in patients with varicose veins, compression treatment, sclerotherapy or surgical removal of veins remain the most effective therapeutic measures in achieving relief of symptoms [1,19]. Currently available drugs do not resolve varicose veins. However, varicose veins are often associated with symptoms of oedema and unpleasant feelings in the legs such as aching in the region of varices, “restless legs” or a feeling of swelling of the lower limbs. They may be resolved by sclerotherapy or surgery. However in many countries “venotonic” drugs are used to manage these problems, moreover in regions of hot weather in which surgeons may abandon surgical treatment during the summer season. Venotonic drugs may be helpful treatment in these cases.

The principal drugs used in Europe are shown in (Table 2).

Micronized Purified Flavonoid Fraction

One of the most frequently used drug groups are the flavonoids. These have been in widespread use in the management of oedema and other symptoms of venous disease for many years [21].

Micronized Purified Flavonoid Fraction (MPFF) (90% diosmin, 10% hesperidin) is a member of the flavonoid family. It has been shown that the intestinal absorption and therefore, bioavailability of this drug may be increased by micronization [21].

Table 1: CEAP classification.

Clinical classification
C0: no visible or palpable signs of venous disease
C1: telangiectasies or reticular veins
C2: varicose veins
C3: edema
C4a: pigmentation or eczema
C4b: lipodermatosclerosis or white atrophy
C5: healed venous ulcer
C6: active venous ulcer
S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A: asymptomatic
Etiologic classification
Ec: congenital
Ep: primary
Es: secondary (post-thrombotic)
En: no venous cause identified
Anatomic classification
As: superficial veins
Ap: perforator veins
Ad: deep veins
An: no venous location identified
Superficial veins:
Telangiectasies or reticular veins
Great saphenous vein above knee
Great saphenous vein below knee
Small saphenous vein
Nonsaphenous veins
Deep veins:
Inferior vena cava
Common iliac vein
Internal iliac vein
External iliac vein
Pelvic: gonadal, broad ligament veins, other
Common femoral vein
Deep femoral vein
Superficial femoral vein
Popliteal vein
Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
Muscular: gastrocnemial, soleal veins, other
Perforating veins:
Thigh
Calf
Pathophysiologic classification
Pr: reflux
Po: obstruction
Pr,o: reflux and obstruction
Pn: no venous pathophysiology identifiable

Table 2: Classification of the main venoactive drugs.

Group	Substance	Origin	Dosage (mg/day)	Dose: how many times a day	
Benzopyrones α -benzopyrones γ -benzopyrones	Coumarin	Sweet clover	90, combined with troxerutin (540)	3	
	Diosmin and micronized purified flavonoid fraction Rutin and O-(β -hydroxyethyl) rutosides: troxerutin	Sweet woodruff			
		Citrus			
		Japanese pagoda tree		1000	1 or 2
		Japanese pagoda tree		1000-2000	
	Eucalyptus spp		1 or 2		
	Buckwheat				
Saponins	Aescin	Horse chestnut	120, then 60	3	
	Ruscus extracts	Butcher'broom	2-3 x 1 tablet	2-3	
Other plant extracts	Anthocyanans	Bilberry	126	3	
		Grape seed	100-300	1-3	
	Oligomeric proanthocyanidins	Marine pine bark	300-360	3	
		Ginkgo	Ginkgo biloba	2 sachets	2
		Calcium dobesilate	Synthesis	1000-1500	2-3
Synthetics	Benzarone	Synthesis	400-600	2-3	
	Naftazone	Synthesis	30	1	

A number of investigations have been undertaken in animals to assess some possible modes of action. MPFF increases venous tone [22,23] and lymphatic flow [24-26]. It also decreases hyperpermeability [27] and increases capillary resistance [28]. These findings may explain why MPFF reduces tissue oedema.

A recent paper has shown that MPFF modified the interaction of leukocytes with endothelium [29]. In a hamster dorsal skin fold model used to investigate the effect of MPFF on the microcirculation following ischemia/reperfusion, the animals pretreated with MPFF exhibited less neutrophil adhesion in postcapillary venules at 30 min, 2 h and 24 h after reperfusion compared with the control group. This observation may well be linked to the protective effect of flavonoids in the treatment of oedema. Decreased leukocyte activation is also associated with decreased platelet and complement system activation, leading to a lowered release of histamine and decreased leukocyte-dependent endothelial damage [30].

The molecular mechanism in leukocyte adhesion and activation in CVD patients involve the increased expression of several types of cell adhesion molecules at the leukocyte surface, particularly L-selectins and integrins [30]. The expression of these leukocyte adhesion molecules were substantially decreased on monocytes and neutrophils after a 60 day treatment with MPFF (C2 to C4) [30,31]. This implies that MPFF would prevent the inflammatory process in CVD.

In patients with CVD as well as after prolonged standing, plasma concentrations of endothelial adhesion molecules, vascular cell adhesion molecule (VCAM) and interstitial cell adhesion molecule (ICAM) are increased [30,31]. In the study by Shoab [31], plasma level of VCAM-1 and ICAM-1 significantly decreased in C₂ to C₄ patients pretreated with MPFF. This reflects the ability of MPFF to prevent the interaction between the endothelium and the leukocytes which is at the core of the CVD progression.

In the reflux assessment and quality of Life improvement, with micronized Flavonoids (RELIEF) study, patients receiving MPFF 500 mg twice daily showed progressive improvement from baseline in the symptoms of CVD [32]. After 6 months, patients in the per-protocol population showed significant improvement from baseline in the study outcome measure (ankle circumference, pain, leg heaviness, cramps, sensation of swelling; (p>0.012). In the year trial of MPFF

500 mg twice daily in 170 patients [33] a significant reduction from baseline values in physician-assessed clinical symptoms (functional discomfort, cramps and evening edema), ankle and calf circumference, and patient overall assessment of symptom severity was demonstrated at each 2-month evaluation.

Then, during the course of a 6-month period of treatment with MPFF 500 mg, chances in the QoL scores were comparable across the different CEAP subgroups [34]. Only patients with symptoms had greater improvement in QoL than patients without symptoms. These changes in QoL scores resulted mainly from the alleviation of symptoms: improvement in pain, heaviness, swelling and cramps was significant for all symptoms [35]. However, the associated signs (teleangectasis, varices, oedema or skin changes did not show such a direct impact on QoL [32].

Other studies demonstrate that MPFF markedly reduced the increased expression of ICAM-1 after 4 hours of reperfusion [35].

MPFF can be used clinically with compliance and no side effects.

Oxerutins

Oxerutins are compounds belonging to the class of flavonoids. Their wide diffusion has stimulated investigation on their biochemical characteristics, which have been identified in their oxide-reductive properties. Oxerutins is a standardized mixture of mono-, di-, tri- and tetra-hydroxyethylrutosides, which are derivative of rutin, a flavonoids extracted from *Sophora Japonica*, a plant used in traditional medicine in China [36].

About 20 double-blind, placebo-controlled studies, enrolling a total of more than 2,000 participants, have examined oxerutins effectiveness for treating varicose veins and venous insufficiency [37-39].

It has been demonstrated that the most important pharmacologic action of oxerutins is the inhibitory effect on microvascular permeability, with a consequent reduction of the formation of edema following the application of several types of injury [40,41]. This effect has been demonstrated in animals and in humans, in controlled, double blind clinical trials, both in healthy volunteers and in patients with CVD [42-43]. Evaluating fluorescence patterns has shown that one of the oxerutins' target organ/tissue is the venous endothelium

[44-46]. The pharmacologic effects of oxerutins appear to be dose-related.

The second pharmacodynamic effect is the ability to modulate the flexibility of erythrocytes membranes [46]. A third pharmacologic effect is the inhibition of the adhesion of neutrophils and platelet to the venous endothelium [45,46].

Oxerutins also act as antagonists and interceptors of free radicals, which cause cellular damage and increase and prolong inflammatory reaction. The antioxidant action of oxerutins on the endothelium membrane and the inhibitory effect on the lipooxygenase are associated with a decrease in capillary permeability (with reduction in edema formation) decrease of local cellular damage caused by free radicals, and reduced adhesion of granulocytes and platelets to the venous endothelium. Therefore, the action of oxerutins at the endothelial levels may improve venous tone [47].

Oxerutins can be used clinically with good efficacy, compliance, and no side effects.

Triterpenic Fraction of Centella Asiatica

Total Triterpenic Fraction of Centella Asiatica (TTFCA) is a natural compound that has been used for many years to treat signs and symptoms associated with venous insufficiency, varicose veins and deep venous disease. Several studies have reported symptomatic relief and a decreased capillary filtration by the administration of the oral preparations [48-52].

In vitro studies have shown that TTFCA can modulate collagen synthesis in cultured fibroblast [49-51] and increase the confluence rate in cultured endothelial cells [52]. An *in vivo* reduction of the number of circulating endothelial cells, which is higher in patients with venous hypertension than in normal subjects, has been shown after 3 weeks of treatment with TTFCA [49]. Previous studies have shown that TTFCA displays microcirculatory effects in patients with venous hypertension, providing an action on the capillary wall and on the interstitial fibrotic component [52].

In the capillary wall TTFCA stabilize the interstitial micro-network that is composed from collagen and elastin, while at the collagen synthesis TTFCA reduces the production of collagenic fibrillar [52]. No side effects are reported.

Aescin

Aescin is the major active principle from *Aesculus hippocastanum* the horse chestnut tree, a plant widely distributed all over the world because of its excellent resistance to environmental conditions [53]. The seeds of *A. hippocastanum* contain a saponin mixture from which two crystalline products can be separated "Aescin" (haemolytic) and "prosapogenin" (non-haemolytic). A number of other products have been isolated from the chestnut seed, i.e. bioflavonoids such as: quercetin, kaempferol and their diglycosyl derivatives, as well as anti-oxidants, such as proanthocyanidin A₂ and the coumarins esculin and fraxin [54]. Aescin is natural mixture of triterpene saponins. The pharmacological profile of β -Aescin has received significant contributions in recent years, in order to establish the pharmacological basis for the major clinical indication of treatment of Chronic Venous Insufficiency (CVD) [55]. At least three types of pharmacodynamic actions have been attributed to

Aescin: 1) anti-oedema properties 2) anti-inflammatory activities 3) venotonic properties. All of these appear to be due to a basic molecular mechanism, identified as a selective vascular permeabilization [55], allowing a higher sensitivity, of e.g. calcium channels, to molecular ions, resulting in increased venous and arterial tone. These sensitizing effects to ions and other molecules, e.g. 5-HT, result probably in the enhanced venous contractile activity, and as a consequence, in the anti-oedematous property of the molecule.

A considerable number of trials have been carried out with oral HCE or Aescin in patients with CVD.

The search by Pittler and Ernst identified 11 randomized clinical trials of Aescin vs placebo, three of which did not reach pre-set minimal quality criteria [56]. In 521 patients observed in the eight placebo-controlled studies given 100-150 mg Aescin daily, generally bid, dosing for 2-8 weeks led to a significant reduction in leg volume and symptoms (pain, fatigue, sensation of tension, itching) compared to placebo. In two of the four trials with reduction in leg volume as primary end-point, the difference vs placebo was clinically significant in two (88-113 ml) and in the remaining two it was of a lesser degree (10-12.7 ml).

A randomized, three-armed controlled trial compared oral Aescin (50 mg bid) with a matching placebo and with a compression therapy in patients with CVD [57]. The 240 selected patients were treated for 12 weeks with either compression stockings class 2, 50 mg Aescin bid, or placebo (one capsule bid) at a ratio of 2:2, 2:1 patients allocated to the compression treatment arm also received a diuretic once daily for 7 days in order to achieve the best possible stocking fit. The statistical analysis concluded that the therapeutic efficacy of Aescin was equivalent to compression therapy preceded by diuretic, and both active treatments were significantly superior to placebo. This study clearly indicates that patients with CVD have a choice between compression therapy, not accepted by more than 50% of patients, as reported in the literature, and by β -Aescin, in order to reduce oedema resulting from chronic venous insufficiency.

In addition to the randomized, double-blind, controlled clinical trials, one further trial is worthy of mention. The National Association of general Practitioners [58] in Germany performed an observational study on the usage of Aescin in CVD. The study assessed the impact of Aescin on symptoms (pain, fatigue, tension, swelling, itching in the legs) and its tolerability profile in clinical practice. Most patients were treated for 4-10 weeks with 45 mg oral Aescin bid. All symptoms improved during the first week of treatment. Also the percentage of patients free of symptoms at the end of treatment increased considerably. Compliance was excellent, being close to 95%.

The overview of studies on CVD clearly concluded that Aescin is effective in controlling oedema and related symptoms in CVD. It is as effective as compression therapy, but better tolerated and more acceptable to patients with no side effects [59].

In a very recent overview of major available treatments for CVD, i.e. Aescin, hydroxylrutoside and MPFF, it has been noted that Aescin appeared to have unique effectiveness, when compared to compression therapy, vs the other two agents and that; furthermore, Aescin appears to exert a progressively better effect during continued therapy [60].

Calcium Dobesilate

Calcium dobesilate (2,5 dihydroxy-benzene-sulfonate), unlike plant extracts, has a precise chemical structure and well-defined pharmacologic properties. It acts on the endothelium and the basal membrane of capillaries, blocking hyper permeability [61], inhibiting platelet aggregation [62], inhibiting blood hyper viscosity [63], increasing red cells flexibility [61], and improving lymphatic drainage [61].

There are numerous published randomized clinical trials [64,65] including a meta-analysis [66], suggesting a beneficial effect of calcium dobesilate in CVD. However, many physicians doubt its efficacy, partly because an important placebo effect has been observed in the pharmacologic treatments of CVD. There are also doubts about its safety since the publication of a case control study that shows an associated risk of Agranulocytosis [61].

Calcium dobesilate administered orally for 4 weeks to patients with CVD significantly improved symptoms like night cramps and discomfort. Studies were not conclusive evidence on the effect of calcium dobesilate on leg volume reduction, pain, paresthesia, and malleolar swelling.

Venous Ulcers

In CEAP classification, C6 represents the condition of active venous ulcer. Usually venous ulcers are treated with compression therapy, but almost 30% of people remain unhealed after 1 year of treatment [67]. Adjuvant to compression treatment could be beneficial. Pentoxifylline, a hemorrheological agent, reduces the viscosity of blood by increasing the flexibility of erythrocytes, encouraging migration of white cells, inhibition of aggregation of platelets and lowering of the viscosity of plasma [68], action that might correct microcirculatory disorders.

Trials [69,70] of the clinical effectiveness of pentoxifylline have had conflicting results and the usefulness of the drug remains unclear [71].

Jull and colleagues reviewed the literature of pentoxifylline used in the treatment of CVD and their results showed that pentoxifylline improves healing rate compared with placebo [72]. Pentoxifylline was effective for treatment of leg ulcers, but the evidence for pentoxifylline on its own is not as strong as that for this drug as an adjuvant to compression treatment [72].

Although which microcirculatory events link venous hypertension with ulceration is not clear, one explanation could be that white cells aggregate and release proteolytic enzymes that damage tissue [73]. Pentoxifylline, which has an inhibitory effect on expression of cellular adhesion molecules [74], could interfere in these processes. The inhibitory effect could be a consequence of the immunosuppressive activity of pentoxifylline on tumour necrosis factor- α (TNF- α) [75]. Expression of cellular adhesion molecules by endothelial cells is upregulated in early venous disease, remains upregulated as the disease progresses, and is accompanied by increased extravasation of leucocytes [76]. Expression of these molecules is regulated by proinflammatory mediators such as TNF- α [77]. Pentoxifylline might also interfere with the production and action of oxygen metabolites [78,79].

Other drugs, such as Glycosaminoglycans (GAGs), as mesoglycan and sulodexide, showed important results in the regulation of endothelial activity moreover in patients with venous ulcers.

Although several pharmacological and surgical strategies are being utilized in the management of varicose vein and CVD with variable success and recurrence rate, inhibition of MMP through sulodexide or mesoglycan 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.

Ultimately, the focus of CVD therapy should move from treating active ulcers to avoiding chronic venous disease progression and ulceration in an effort to reduce the socioeconomic cost incurred by this disease [80]. The beneficial effects on venous pressure and the signs and symptoms of CVD indicate that glycosaminoglycans (GAGs) as Sulodexide and Mesoglycan are a useful treatment option for the prevention of venous ulcers, but this indication should be formally investigated [9]. The anti-inflammatory activity of GAGs and their effects on preserving and restoring endothelial function and restoring a good balance between matrix metalloproteinase and their tissue inhibitors suggest that this therapy may reduce or prevent the pathophysiological changes leading to the development and progression of venous ulcers [81,82]. Clinical studies of GAGs have shown that the agent is associated with significant improvement of the clinical signs and symptoms of venous ulcers, and is therefore a recommended therapy in combination with local wound care and bandages for patients with persistent venous leg ulcers [83].

Conclusion

Chronic venous insufficiency is a serious social and medical problem.

Although clinical and basic science research over the last years have produced new development in several areas of CVD, there is still no consensus regarding definition, optimal diagnostic technique and treatment strategies for CVD [84].

Actually, the therapeutic strategies in the treatment of CVD include physical methods, such as elevation of the leg, compression therapy with bandages or elastic stockings, sclerotherapy, surgical correction of superficial or perforating vein incompetence where appropriate and drug treatment.

In CVD, the major pathological event is venous hyper pressure. Venous hypertension is a consequence of venous reflux caused by venous valvular insufficiency. The actual causes of venous insufficiency remain unknown, with the exception of the post-thrombotic syndrome, where there is clear evidence of vessel abnormalities and of valve destruction [80].

The high venous pressure, either in the superficial or in the deep venous system, overloads the capillary network [85] which is the crucial factor in the pathogenesis of all the complications of venous disorders. The importance of microcirculatory changes in severe complications of venous disease has been stressed [86,82]. The main pathophysiological feature appears to be activation of the leukocytes, followed by margination and interaction of these cells with the macrovascular endothelium, resulting in the preferential accumulation of neutrophils in the tissue. This initiates

an inflammatory response releasing free radicals and other cytotoxic substances that may lead to tissue destruction and ulceration and, clinically, to the chronic changes seen in stasis dermatitis [87]. All these pathophysiological alterations could be expressed clinically by symptoms such as pain, leg heaviness, paresthesia, restless legs and nocturnal cramps and signs as teleangiectasia, reticular and varicose veins and skin changes (pigmentation, lipodermatosclerosis, eczema and ulceration).

It has, then, become clear that both macro circulatory and microcirculatory alterations represent the pathophysiological events in CVD that should be target by therapy.

Compression therapy and surgical procedures is mainly target towards the macro circulatory alterations, while Phlebotonic drugs can act both on the microcirculatory and macro circulatory alterations at the same time. The application of such measures may reverse or stop the inflammatory process.

Oral Phlebotropic drug are widely used in the management of patients with CVD. They might sometimes completely resolve a symptom of CVD, but the usual outcome appears to be an improvement in CVD rather than a cure.

Then, the combination of compression therapy and the use of one of the many Phlebotronic drugs would probably be more effective than one therapy alone [88].

The main cornerstone of treatment of CVD is represented by the venoactive drugs such as MPFF and GAGs; for these drugs it is possible to propose a strong recommendation for their use in the therapy of advanced stages of CVD, examining the different guidelines based on evidence [89-90].

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