PHARMACEUTICAL THERAPY OF CHRONIC VENOUS DISEASE

MEDIKAMENTNA TERAPIJA HRONIČNE VENSKE BOLESTI

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Summary

Chronic venous disease (CVD) is a common condition and a global phenomenon that affects a significant part of the population worldwide. The majority of patients with CVD have symptoms that significantly affect their daily activities and deteriorate the quality of their life. Treatment modalities vary from medical and other types of conservative therapies, less invasive endovenous intervention to radical surgical procedures. The purpose of this article is to underline the importance of venoactive drugs in the treatment of patients with CVD.

Key words: CVD, pharmaceutical therapy, venoactive drugs

Apstrakt

Hronična venska bolest je često stanje i globalni fenomen koji utiče na značajni deo svetske populacije. Najveći broj pacijenata koji boluje od hronične venske bolesti, ima simptome koji u značajnoj meri utiču na njihove dnevne aktivnosti i narušavaju njihov kvalitet života. Modaliteti lečenja variraju od medikamentne i ostalih tipova konzervativne terapije, preko minimalno invazivnih endovenoznih procedura do radikalnih hirurških procedura. Cilj ovog rada je da se podvuče značaj venoaktivnih lekova u tretmanu pacijenata sa hroničnom venskom bolešću.

KLjučne reči: hronična venska bolest, medikamentna terapija, venoaktivni lekovi

INTRODUCTION

Chronic venous disease (CVD) is a common condition and global phenomenon that affects a significant part of the population worldwide (1). CVD includes the full spectrum of morphological and functional abnormalities of the venous system irrespective of whether they produce any symptoms.

The grading of chronic venous disorders (CVD) was simplified and standardized by the introduction of the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification system (2). The CEAP classification categorizes limbs into seven classes from C0 to C6. Each clinical class is further characterized by the subscript (S) if the categorized limb is symptomatic or the subscript (A) if the limb is asymptomatic. The international character of CEAP classification allows precise comparisons between countries and continents.

It has to be noted that the majority of patients with CVD have symptoms that significantly affect their daily activities and deteriorate the quality of their life. However, it is not easy to confirm a positive correlation between signs and symptoms of CVD. CVD could be associated with a whole range of symptoms such as: pain, heaviness, restless legs, tingling, aching, burning, night muscle cramps, swelling, sensations of throbbing or itching skin, leg tiredness and/or fatigue (3). In addition, these symptoms could be a part of some other non – venous chronic and acute diseases and conditions: obesity, neurological reasons, standing or sitting professions, or arterial occlusive disease (4).

In addition to others, a very specific group of patients has been isolated in recent years. These patients have no visible signs of disease, but they are constantly reporting venous – like symptoms and are thus a real “nightmare” for both GPs and vascular surgeons (2, 5, 6). There are approximately 20% of patients with CVD in C0s category and identification of these patients could be crucial from diagnostic and therapeutic point of view.

Along with CVD pandemic, a different treatment modality has been developed in order to deal with and control the disease in the early stages.

Treatment modalities vary from radical surgical procedures, over less invasive endovenous interventions, to medical and other types of conservative therapies.

The purpose of this article is to underline the importance of venoactive drugs in the treatment of patients with CVD.

PHARMACEUTICAL THERAPY OF CVD – VENOACTIVE DRUGS

Veno-active drugs (VADs) constitute a diverse group of medications, which are synthetic but mostly have herbal origin. Five main types of VADs have been identified (7):

1. Alpha – benzopyrones, notably coumarin;
2. Gamma – benzopyrones, also known as flavonoids,

- which include simple diosmins, micronized purified flavonoid fraction (MPFF), and the rutosides, including rutin, troxerutin, and hydroxyethylrutosides (Hr);
3. Saponins, including horse chestnut seed extract (HCSE) and ruscus aculeatus extract;
 4. other herbal extracts, including anthocyanins, proanthocyanidins (grape seed extract, red-vine – leaf extract), *Ginkgo biloba* extract, and *Centella asiatica* extract;
 5. synthetic products (chemical family of quinons) which include naftazone and calcium dobesilate.

Due to diversity of VADs, there are multiple mechanisms of their action (7):

- The most important mechanism of action is their impact on inflammatory processes in venous valves and the vein wall: scavenging of free radicals, blocking the propagation of oxidative reactions and reinforcing inherent cellular antioxidant capacity. Notably MPFF has a significant anti – inflammatory effect in the early stage of inflammatory cascades: by inhibiting leukocyte – endothelial interactions;
- Actions on venous tone – most of them act by modulating noradrenergic signaling, by reducing nor-epinephrine metabolism in the cases of MPFF and hydroxyethyl-rutosides or by agonism of venous $\alpha 1$ -adrenergic receptors in the case of *Ruscus* extracts;
- Actions on capillary permeability (edema) – with their antioxidant and anti – inflammatory effects, it is not surprising that many of the major VADs have been shown to reduce capillary hyperpermeability, MPFF treatment significantly reduces plasma VEGF in patients with skin changes, and plasma VEGF has been proposed as a marker of MPFF therapy;
- The positive effect on lymphatic circulation and lymph flow;

Reduction of blood viscosity and improvement in blood flow – several VADs have been shown to reduce blood viscosity and/or erythrocyte aggregation, including MPFF, troxerutin and calcium dobesilate.

THE PLACE OF VENOACTIVE DRUGS IN DAILY CLINICAL PRACTICE

The concept of venoactive drugs is more than attractive. According to a perfect scenario, VADs could reduce progression of CVD, symptoms related to CVD and even development of severe stages and the occurrence of venous ulcers and all the accompanying complications.

In recent guidelines, only some of VADs have found their place in the management of CVD (7,8). (Table 1)

Recommendations for the use of venoactive drugs in guidelines are based on the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) system (9, 10). The GRADE system differs from other schemes described in the guidelines in the fact that separate levels are assigned for the recommendation of treatment and for the quality of evidence on which the recommendation is based. Recommendations are classified as either strong (grade 1) or weak (grade 2), and quality of evidence as high (grade A), moderate (grade B) or low (grade C). Importantly, the GRADE system recognizes that large observational studies may provide evidence of moderate or even high quality, particularly if the estimation of the magnitude of the treatment effect is very large. In current clinical practice, the major point of interest concerning these drugs is to reduce symptoms related to CDV.

Table 1. Recommendations for venoactive drugs from the international consensus meeting in Cyprus, November 2012.

Indication	Venoactive drug	Recommendation	Quality of evidence	Grade
Relief of venous symptoms (C0 _s to C6 _s) and edema (C3)	MPFF	Strong	Moderate	1B
	Simple diosmins	Weak	Poor	2C
	Rutosides (O-betahydroxyethyl)	Weak	Moderate	2B
	Calcium dobesilate	Weak	Moderate	2B
	HCSE	Weak	Moderate	2B
	<i>Ruscus</i> extracts	Weak	Moderate	2B
	<i>Ginkgo biloba</i>	Weak	Poor	2C
	Other VADs	Weak	Poor	2C
Adjunctive treatment of primary venous ulcer (C6)	MPFF	Strong	Moderate	1B

MICRONIZED PURIFIED FLAVONOID FRACTION (MPFF) TREATMENT STRATEGY

Micronized purified flavonoid fraction has a number of vein – specific anti – inflammatory effects that relieve symptoms at all stages of CVD. In several placebo – controlled trials, MPFF was associated with a significantly greater improvement in many of the symptoms of CVD after 2 months compared to placebo ($P < 0.001$ MPFF versus placebo) or simple diosmin ($P < 0.05$ MPFF versus simple diosmin). Moreover, symptom relief with MPFF was achieved rapidly and maintained in the long term (11).

In a meta-analysis of 459 patients, MPFF significantly reduced the symptoms associated with venous ulcers after 4 and 6 months of the treatment (12). MPFF is also beneficial for post – surgery pain, (13, 14, 15) and the pain associated with pelvic congestion syndrome (16). Patients receiving MPFF 2 weeks before and continuing for 14 days after varicose vein surgery required significantly less analgesic use than the control group (13, 14). In a cross – over study, women were randomized to receive either MPFF or placebo. After 6 months, mean pain scores were significantly lower in the MPFF group compared to placebo ($P < 0.05$) (16).

In recent guidelines for the management of CVD, MPFF has been assigned a high level of recommendation as a first – line treatment for venous symptoms in any stage of CVD (7). It should be noted (Table 1) that the recommendation for MPFF is strong, based on benefits that clearly outweigh the risks and evidence of moderate quality (grade 1B) for the indication of relief of venous symptoms in C0_s to C6_s patients, including those with CVD – related edema. MPFF retains its strong recommendation for use as adjuvant therapy in treating venous ulcers (7).

In conclusion, CVD is a global phenomenon that has almost pandemic proportions. In order to deal with this massive phenomenon, several therapeutic options have been developed. Apart from very popular surgical and less invasive procedures, venoactive drugs have been trying to find their place on the global medical scene for many years. Today, latest guidelines have started to recommend venoactive drugs, especially MPFF, as a standard symptom relief therapy, in every stage of CVD. However, promising beneficial effects and expansion of their use are yet to be explored in further multicenter trials.

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