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REVIEW ARTICLE

The Significance of Pain in Chronic Venous Disease and its Medical Treatment

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Abstract: Chronic venous disease (CVeD) is a highly prevalent condition in the general population, and it has a significant impact on quality of life. While it is usually manifested by obvious signs, such as varicose veins and venous ulcers, other symptoms of the disease are less specific. Among the other symptoms, which include heaviness, swelling, muscle cramps and restless legs, pain is the symptom that most frequently compels CVeD patients to seek medical aid. However, there is a substantial discrepancy between pain severity and clinically detectable signs of CVeD, questioned by several opposing studies. Further evaluation is needed to clarify this subject, and to analyse whether pain development predicts objective CVeD progression.

General management of CVeD starts with advising lifestyle changes, such as lowering body mass index and treating comorbidities. However, the mainstay of treatment is compression therapy, with the additional use of pharmacological substances. Venoactive drugs proved to be the drugs of choice for symptom alleviation and slowing the progression of CVeD, with micronized purified flavonoid fraction being the most effective one. Interventional therapy is reserved for advanced stages of the disease.

Keywords: Chronic venous disease, pain, venoactive drugs.

INTRODUCTION

Chronic venous disease (CVeD) is a condition caused by dysfunction of any of the normal structures of the superficial venous system that may lead to venous hypertension and development of venous insufficiency. It is estimated that CVeD affects >30% of the adult population in the Western world and bares significant economic burden [1]. Also, more advanced sequelae of CVeD, such as venous ulceration, are seen in approximately 1% of adult population [1, 2].

Although most of the risk factors for CVeD are acknowledged and include heredity, age, female sex, obesity, pregnancy, prolonged standing, and lack of physical activity, its basic aetiology is still unclear [3, 4]. The most frequent cause of CVeD mentioned in the literature is either primary abnormality of the venous wall and valves, or secondary changes derived from previous venous thrombosis that leads to reflux, obstruction or both. Congenital venous malformations are a rare cause of CVeD [5].

While CVeD is usually manifested by obvious signs, such as varicose veins and venous ulcers, the symptoms of the disease are less specific. In order to standardize the evaluation of CVeD, the first CEAP (clinical, etiologic, anatomic, pathophysiologic) consensus document was issued after the American Venous Forum meeting in 1994, and underwent revision in 2004 [6, 7]. Since then the CEAP classification has been widely used in the literature and proved appropriate for establishing recommendations, however, some papers pointed out the inconsistency of association between its C class and the degree of symptoms, especially pain [8].

Among the other symptoms, which include heaviness, swelling, muscle cramps and restless legs, pain is the symptom that most frequently compels CVeD patients to seek medical aid [9]. In addition, several studies showed that CVeD pain has a major impact on quality of life [10, 11]. However, the main drawback in recognizing venous pain is its similarity to sensations caused by other common conditions [9].

We review the subcellular origin of venous pain, the correlation of pain with clinically detectable signs and its medical treatment in patients with CVeD.

PAIN MECHANISM IN CVeD

Veins are innervated by sensory nerve fibres, which originate in the dorsal root ganglia of the spinal cord. Some of these sensory fibres end in the venous wall between endo-

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thelial cells and smooth muscle cells, while others reach the perivenous space, where they are in close contact with vasa vasorum. The latter nerve endings are polymodal nociceptors [12, 13].

At first, it was speculated that venous dilation is sufficient to cause strong painful sensations. However, experiments with mechanical venous balloon dilation showed that painful sensations are felt when the diameter of a vein reaches 3 times its normal value, which would not correspond to venous pain intensity in real-life conditions [14, 15].

More recent hypotheses on the origin of CVeD pain are based on a local inflammatory reaction, related to venous stasis [12]. Particularly, persistent venous hypertension evokes a local inflammatory response mediated by leukocytes, involving a cascade reaction of cytokines and chemokines and altered endothelial function [16].

Initially, hypoxic conditions, present during venous stasis, activate the endothelial cells [17]. Their activation starts with accumulating calcium in the cytoplasm, which in turn upregulates phospholipase A2 activity. The subsequent enzyme cascade leads to the synthesis and release of local mediators, such as bradykinin, platelet-activating factor (PAF), prostaglandin E2 and leukotriene B4. PAF stimulates local release of histamine and serotonin, which cause abnormal adherence of leukocytes to the venous endothelium, and further augments the inflammatory process [17, 18]. Finally, most of the above-mentioned proinflammatory mediators stimulate the nociceptors in the venous wall and perivenous tissue, and thus produce pain sensations.

On the other hand, the theory of 'white cell trapping' suggests that elevated venous pressure and subsequent stasis cause leukocyte margination, activation, adhesion and extravascular migration, conveyed by a set of cytokines and vascular adhesion molecules. Saharay *et al*. investigated leukocyte endothelial adhesion in patients with CVeD who were subjected to short-term venous hypertension [19]. They showed that plasma levels of the endothelial adhesion molecules were higher in patients with CVeD than in control subjects, and increased significantly in response to venous hypertension provoked by standing. Another study found positive correlation between expression of selected cytokines and venous haemodynamics in different CVeD stages. In addition, the authors proposed a potential role of selected cytokines, such as endothelial growth factor (EGF) and platelet derived growth factor (PDGF), as biomarkers of disease progression and recurrence rates during postsurgical monitoring [20].

DISCREPANCY BETWEEN SYMPTOMS AND CLINICAL SEVERITY OF CVeD

Staging of CVeD is based on the last revision of the CEAP classification [21]. Its clinical importance is based on correct diagnosis and it serves as a guide for a regular clinical examination of patients with CVeD. Also, it helps in a decision-making process for selecting the appropriate treatment [22]. Each clinical class in CEAP system is characterized by the presence or the absence of symptoms (Table **1**). However, the association of occurrence and intensity of symptoms with C (clinical) class of the CEAP classification is largely inconsistent [23].

Firstly, some conditions can mimic CVeD symptoms in healthy individuals by inducing transient venous stasis and hypoxia, and thus making the proper diagnosis difficult [24]. Blatter *et al*. investigated leg symptoms in 46 healthy subjects during prolonged standing [25]. The results showed that prolonged standing lead to increased leg volume and provoked pain in the majority of subjects. However, they found no correlation between the volume increase and the resulting symptoms. Peripheral arterial disease, knee or hip arthrosis, and spinal disc herniation can also cause symptoms similar to CVeD, such as sensation of heaviness, swollenness, leg discomfort and pain [26]. It is mandatory to exclude these conditions before treating for CVeD, especially in symptomatic patients without any visible signs of the disease.

Additionally, what may explain the discrepancy between pain and signs of CVeD is that different duration of the same process is required for developing both, painful sensations and pathological remodeling of venous vessels. Pain could be a short-term consequence of venous hypertension, so it may be considered as an early predictor of CVeD, while in contrast, visible varicose vein remodeling is a much later outcome of the same process. Several studies suggested that the primary activation site of venous and perivenous nociceptors may not be in the large veins [27, 28]. Strictly speaking, microvalvular incompetence could exist in the small superficial veins of the leg independently from the great saphenous vein or its major tributaries [29]. In addition, contact between nerve endings and veins at that level probably is tighter than at the macrovascular level. That being said, it is possible that the primary activation site of nociceptors could be in the microcirculation, thus explaining the occurrence of pain before any visible signs of CVeD [30].

The literature concerning relation between leg pain and clinical severity of CVeD is inconsistent. The majority of studies which observed positive correlation between C grade of CEAP classification and the degree of pain, also noted venous-like symptoms in high number of control subjects without CVeD. The Edinburgh vein population study found correlation between some of the reported symptoms and the presence of great and small saphenous vein varices, but mostly in women [31]. However, the level of agreement between the presence of symptoms and trunk varices was not significant. The authors came far to conclude that most symptoms probably have a non-venous cause, even in the presence of trunk varices. In a cross-sectional study including 2841 patients with CVeD, severity of pain differed significantly throughout the C class [8]. Light and moderate pain gradually decreased, while severe pain gradually increased from C0 to C6 class, even after the adjustment for age, body mass index (BMI) and family history of CVeD. An international cohort study of 1531 patients with CVeD, reported that physicians' assessment coincided with patients' own perception of the disease [32]. However, the intentional oversampling the study population with male patients and patients with venous ulcers might have had some impact on the generalizability of the study results. Chiesa *et al*. demonstrated a positive correlation between the presence of symptoms with both worsening of the visible signs and the pres-

Table 1. C class of the CEAP (clinical, etiologic, anatomic, pathophysiologic) classification.

Class	Definition
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins; differ from reticular veins by a diameter of 3 mm or more
C3	Oedema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease, divided into two subclasses: C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer
S	Symptomatic; including pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic

ence of haemodynamic changes in the leg venous system [33]. Venous reflux was associated both with increase in C grade of visible disease, and with presence of symptoms. In addition, there was a considerable number of symptomatic patients with no visible signs of the disease. The San Diego population study showed that venous symptoms were more prevalent in people with both visible and functional abnormalities, with pain being the most reported symptom [34]. However, pain was relatively non-specific, as it was also reported by 15% of study participants without CVeD.

Furthermore, some other studies did not find a correlation between symptoms and visible signs of CVeD. In a study with 400 patients, Conway *et al*. concluded that CVeD symptoms are independent of disease severity assessed by the CEAP score. Although, they showed positive correlation between pain and saphenofemoral or saphenopopliteal junction reflux [35]. Duque *et al*. found that pain, itch, and burning sensations are common symptoms of mild to moderate CVeD, with a significant impact on quality of life [36]. There was no correlation between the severity of these symptoms and the degree of CVeD. However, the participants were primarily hospital employees, who are more likely to develop venous symptoms [37]. In an observational study of 132 patients with CVeD, no correlation was found between patient-reported symptoms and clinical stages from C2 to C5 [38]. Conversely, patients with C2 and C3 grade reported more severe symptoms than patients with C4 and C5 grade. Also, pain and heaviness were scored highest by the patients with C2 and C3 grades. The explanation proposed was that patients with severe stages of CVeD suffer from sensory peripheral neuropathy, which may result in less pain.

Sensory peripheral neuropathy is a feature of severe CVeD, which could explain the decrease in frequency and intensity of pain in advanced stages of the disease [39, 40]. It is contemplated as a consequence of increased endoneural pressure and ischaemia, secondary to venous microangiopathy. There is a significant threshold elevation for tactile, vibrational and thermal sensations in the extremities in patients with CVeD [41]. Padberg *et al*. compared sensory thresholds in the limbs of patients with C2 grade with the ones with C5 grade, and found that thresholds at the most common sites of venous ulcerations were significantly higher in patients with more severe stages of CVeD [41]. Also, the distribution of sensory neuropathy was coincident with trophic changes of the leg.

Lastly, the complexity of pain generating mechanism permits interindividual variability in pain presentation among patients suffering from CVeD [12]. This variability can be explained on several different levels of pain signal transmission: the reactivity of the cells mediating the local inflammatory process, the density of venous and perivenous innervation, and the density of nociceptors' ion channels; all of which vary considerably from one individual to another [42]. In addition, the intensity of brain modulation of nociceptive sensations is also unequal, mostly due to genetic factors.

MANAGEMENT OF SYMPTOMATIC CVeD

As CVeD is not a critical condition in its early stages (C0-C2), its initial management is often ambulatory and in primary care settings. It consists of advising lifestyle changes and providing information about possible future symptoms and complications.

Obesity is probably the main modifiable risk factor for symptomatic CVeD [43, 44]. Metabolic syndrome present in obese patients promotes a chronic inflammatory environment in the adipose tissue throughout the body, which further aids in the development of venous thrombosis, the main secondary cause of CVeD [45]. In addition, adipocytokine action, impaired coagulation cascade and increased oxidative stress, all present in patients with higher BMI, assist the thrombotic process in superficial veins of the lower extremity [46]. On the other hand, elevated intra-abdominal pressure in obese patients leads to higher risk of reflux, and subsequently venous hypertension, which accelerates CVeD progression [46,

47]. Unfortunately, the majority of studies analysing CVeD treatment specifically excluded overweight people, and attributed their symptoms to musculoskeletal difficulties [48]. Nevertheless, dietary advice should not be disregarded in treatment of CVeD.

As CVeD is a wide-range population disease, it is often coexistent with other chronic conditions [29]. In a cross-sectional study of 1679 patients, the authors associated a number of comorbidities with CVeD symptoms in both genders, such as diabetes mellitus, arterial hypertension, heart failure, skeletal and joint leg disease and chronic obstructive pulmonary disease [49]. In addition, the same chronic conditions were risk factors for venous ulceration development [50]. Therefore, early recognition and treatment of comorbidities could reduce symptoms and deter progression of CVeD.

Due to the progressive nature of the disease, at about 2% per annum from C2 to higher categories [51], the point of referral to vascular specialists for a more targeted treatment is crucial [52]. According to actual guidelines on CVeD management, the presence of symptoms, such as pain, discomfort, heaviness and itching, is an indication for such a referral [53, 54].

Thereafter, primary diagnostic evaluation of CVeD should be performed with duplex ultrasound, since it is a gold standard and provides sufficient data on anatomical distribution of thrombosis and reflux in the venous system of the lower extremities [55, 56]. Also, air plethysmography can be used in selected cases which require more detailed information [57, 58]. The severity of findings in addition to presented clinical picture defines further management of CVeD. Accordingly, interventional approach is considered for treatment of advanced stages of CVeD, while more conservative treatment includes compression and pharmacological therapy [55].

Compression therapy is first-line treatment for patients with symptomatic CVeD, which has been employed since the time of Hippocrates and Celsus [59, 60]. Its principle is to exert a controlled mechanical pressure on the surface of the affected limb, and thus counteract the pathologically increased hydrostatic pressure in its superficial venous system. By doing so this action reduces vein diameter and increases venous blood flow [61, 62], and thus alleviates the symptoms of CVeD. However, one should bear in mind that compressive therapy does not address the problem of obstruction and reflux, if one exists.

There are several types of compression bandages and stockings in different lengths, all of which were positively evaluated through different trials [63-66]. Various grades of pressure (20-60 mmHg) are applied in accordance to the severity of the disease. However, a Cochrane Database systematic review concluded that even though the symptoms subjectively improved with wearing stockings across the included trials, the inadequate reporting and a possible subject to bias demote the quality of existing evidence [67]. Patients with concomitant arterial disease of the lower limbs require extreme caution in administering compression therapy, and additional evaluation is mandatory [68]. Another important issue concerning compression therapy is poor compliance due to discomfort and inconvenience, which ranges 40-70% throughout different studies [69-71].

Pharmacological therapy mostly targets patients complaining of leg symptoms, but without any visible signs of CVeD (C0s class). Venoactive drugs (VAD) emerged as substances which counter the inflammatory process in venous tissue [5]. In addition to their anti-inflammatory effect, VADs increase venous tone and capillary resistance, improve lymphatic flow, and reduce blood viscosity and erythrocyte aggregation [72, 73]. Most importantly, they showed significant benefit in CVeD symptom management in placebo-controlled studies [72, 74].

There are 5 main types of VADs [74]:

1. Coumarin
2. Flavonoids: diosmins, micronized purified flavonoid fraction (MPFF) and rutosides
3. Saponins: horse chestnut seed extract (HCSE) and ruscus aculateus extract
4. Other plant extracts: anthocyans, proanthocyanidins, and extracts of Ginko biloba and Centella asiatica
5. Synthetic products: naftazone, and calcium dobesilate.

MPFF is a composition of diosmine and flavonoid components used both for venous symptom relief and ulcer healing, according to GRADE system recommendation [75, 76] (Table **2**). Its most important vein-specific anti-inflammatory effect is leukocyte trapping inhibition, which in turn reduces cytokine release [77]. In addition, it inhibits noradrenalin degradation, and thus indirectly increases venous tone [72]. The RELIEF study, which included 5052 CVeD patients graded C0-C4, reported of significant reduction of pain, heaviness and cramps in the lower extremities, during the 6-month MPFF therapy period [78]. On the other hand, a prospective randomized placebo-controlled trial showed significant improvement in managing night cramps, without effect on any other CVeD symptoms [79]. Nevertheless, a Cochrane systematic review from 2016 concluded that MPFF is the most effective VAD in reducing CVeD symptoms [80], while another recent systematic review found evidence to support the use of MPFF for medical treatment of CVeD [81]. Lastly, MPFF is also prescribed for pain management and haematoma resorption after phlebectomy [82].

The remaining VADs did not prove to be as effective as MPFF in treatment of CVeD, although they were mostly investigated in smaller studies. Oxerutins and rutosides are flavonoids, which decrease capillary permeability and reduce free radical formation [83]. A prospective randomized placebo-controlled study of 60 patients showed effectiveness of oxerutins in controlling venous hypertension and alleviating CVeD symptoms [84]. Another small prospective study compared the effects of oxerutins and MPFF on patients with symptomatic CVeD. Oxerutins were even more efficient than MPFF in symptom control and improved general quality of life in study participants [85]. As for the rutosides, a meta-analysis including 15 studies of limited quality concluded that hydroxyethylrutosides significantly reduced symptoms of pain, heavy legs and cramps, without any serious adverse events [86]. The same drug reportedly reduces

Table 2. Recommendations for relief of symptoms associated with chronic venous disease according to GRADE system. MPFF – micronized purified flavonoid fraction, HCSE – horse chestnut seed extract.

Venoactive Drug	Recommendation for Use	Quality of Evidence	Grade
MPFF	Strong	Moderate	1B
Rutosides	Strong	Moderate	1B
Calcium dobesilate	Weak	Moderate	2B
HCSE	Weak	Low	2C
Ruscus extracts	Weak	Low	2C

the incidence of superficial venous insufficiency in patients with reduced calf muscle pump dysfunction [87].

HCSE has both anti-inflammatory and anti-oedematous properties, as well as positive effect on the venous tone and blood coagulability [88]. A recent review analysed the results of randomized controlled trials which tested the effectiveness of HCSE in CVeD treatment. The results showed that HCSE significantly reduces symptoms, such as pain, muscle spasm, itch and fatigue, while it tested similarly when compared with compression therapy and rutosides [89].

Contrary to other VADs, calcium dobesilate is a synthetic drug which affects platelet aggregation, capillary permeability and blood viscosity, and showed promising results in treatment of CVeD [90]. In a prospective randomized placebo-controlled study of 256 patients, calcium dobesilate reduced leg oedema and improved CVeD symptoms, both independently and concomitant to compression therapy usage [91].

Interventional therapy should be considered when symptom relief is not accomplished, or when complications occur despite well-timed non-invasive therapy. Several treatment options are offered: sclerotherapy, endovenous thermal ablation and open surgery. Sclerotherapy is applied for obliteration of telangiectases, small-diameter varicose veins and venous segments with reflux [92]. Laser or radiofrequency thermal energy is used for ablation of incompetent veins, and is considered a worthy less-invasive alternative to open surgery [92]. Although, numerous comparative studies showed slight advantage of endovenous therapy over open surgery, the latter is still reserved for the most advanced cases [93,94,95].

CONCLUSIONS

Pain is the most important symptom in patients suffering from CVeD and it has a significant impact on quality of life. However, as other conditions can produce similar sensations, it is difficult to evaluate the true incidence of venous pain, especially in subjects without visible signs of the disease. Also, there is a substantial discrepancy between pain severity and clinically detectable signs of CVeD. Further studies are needed to clarify this subject, and to evaluate whether pain development predicts worsening of CVeD.

General management of CVeD starts with advising lifestyle changes, such as BMI correction, and treating comorbidities. According to all the guidelines on CVeD treatment, the development of symptoms requires referral to a vascular specialist. Thereafter, the mainstay of CVeD management is compression therapy, with the additional use of pharmacological substances. VADs proved to be the drugs of choice for symptom alleviation and slowing the progression of CVeD, with MPFF being the most effective one. Interventional therapy is used in patients with unsatisfactory response to conservative treatment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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