Comparison of Pycnogenol® and Daflon® in Treating Chronic Venous Insufficiency: A Prospective, Controlled Study

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The evolution of microcirculatory methods and the definition of the concept of venous microangiopathy allow to study in a quantitative way microcirculatory changes produced by pharmacological treatments at the areas most frequently and severely affected by chronic venous insufficiency (CVI), venous hypertensive microangiopathy (VHM) and venous ulcerations (1–7).

The evaluation of the effects of treatments on edema and on the microcirculatory changes associated with CVI and venous microangiopathy is possible by evaluating dynamic microcirculatory parameters and capillary responses by noninvasive tests such as laser Doppler flowmetry (LDF) (7–12).

These noninvasive tests can be repeatedly performed to evaluate the quality and rapidity of action of venous treatments on signs/symptoms.

In subjects with CVI and venous microangiopathy the skin flux at rest in the perimalleolar region (RF) is generally increased (1–8). The venoarteriolar response—defined as the reflex vasoconstriction measured after the passage from the supine to the standing position—is irregularly altered, often decreased. Other microcirculatory changes, depending on the degree of CVI and its duration, may be present.

In advanced phases, transcutaneous \( \text{PO}_2 \) is decreased, \( \text{PCO}_2 \) is increased, and capillary filtra-

\[ \text{PO}_2 \text{ and } \text{PCO}_2 \text{ values in the Pycnogenol group. A significant level of improvement was reached after 4 weeks of treatment in most patients (p < .05) of the Pycnogenol group while clinical improvement was significant only in 6 subjects in the Daflon group. The positive effects of treatment with Pycnogenol after 8 weeks were significantly larger in comparison with the Daflon group. In conclusion, this study confirms the fast clinical efficacy of Pycnogenol in patients with chronic venous insufficiency and venous microangiopathy and its superiority—considering the evaluated parameters—to the combination of diosmin and hesperidin.} \]

**Key Words:** Venous microangiopathy—Edema—Pycnogenol®—Diosmin and hesperidin—Daflon—Venous disease—Chronic venous insufficiency—Varicose veins.
tion—clinically visible as edema, and measurable with strain-gauge plethysmography—is greatly enhanced (3–12).

These parameters may change in days and even hours if and when influenced by factors as environment, temperature, protracted standing, exercise, and when appropriate treatment is used (13–20).

Pycnogenol®, a standardized extract from the bark of the French maritime pine, consists of polyphenols, predominantly procyanidins and phenolic acids (21). Pycnogenol has demonstrated its efficacy and safety in several clinical trials. Symptoms of chronic venous insufficiency, such as cramps, pain, feeling of heavy legs, and edema have been reduced significantly by Pycnogenol in controlled studies (22–24). A comparative study showed higher efficacy in reducing CVI symptoms compared to another products based on horse chestnut extract (25). Addition of Pycnogenol to a troxerutin preparation enhanced the activity of the preparation in treating CVI symptoms (26). Recent studies demonstrated protection against edema formation (27) and thrombosis (28) in long haul flights.

The association of diosmin and hesperidin (Daflon®) is a combination of diosmin 450 mg and flavonoids (expressed as hesperidin, 50 mg) in 500 mg tablets, has been used in several clinical trials to fight symptoms of CVI (29–32). Some 12 comparable preparations of this combination product are available (33).

The aims of this prospective study were to compare the efficacy of Pycnogenol and Daflon, on signs and symptoms—and on selected microcirculatory parameters—of severe CVI in subjects with severe venous hypertension.

**PATIENTS AND METHODS**

**Inclusion Criteria**

Evaluation methods for chronic venous disease, venous hypertension, and microangiopathy described in this article have been reported in previous publications (1–12). Venous reflux in the popliteal vein had been shown—before inclusion—by color duplex. The increase in venous pressure had been measured by AVP (1–3) (ambulatory venous pressure). Arteriovenous pressure (AVP) (3,4) was significantly increased in all patients at inclusion being higher than 55 mm Hg in all included limbs due to combined superficial and deep venous incompetence. AVP values after exercise were not completely normal-

ized by a tourniquet excluding the superficial venous system (this indicated combined, superficial, and deep venous incompetence). Varicose veins and superficial venous incompetence in all studied limbs were associated with deep venous incompetence (most of venous hypertension was actually due to deep incompetence).

**Exclusion Criteria**

No other clinical cardiovascular disease requiring treatment was present. Diabetic patients, and patients with bone or joint disorders and any systemic disease requiring medical treatment were excluded. We also excluded, with the use of ultrasound, the presence of recent thrombosis. Patients with a confirmed or even suspected clinical history of thrombosis in the previous 24 months were excluded.

**Treatment**

Patients were randomized to treatment with 150 or 300 mg Pycnogenol or 1000 mg Daflon. Patients received either Pycnogenol 50 mg capsules, 3 times daily, for a total of 150 mg daily or 300 mg Pycnogenol daily for 8 weeks. The comparative group received 1000 mg Daflon as 500-mg tablets, twice daily. Treatment groups were comparable in terms of age and male/female ratio (Table 1).

Compression stockings were not used during the study (and for at least 1 week before inclusion). The study was conducted in summer when signs and symptoms due to CVI are more significant and when it is difficult to wear stockings for the high daily temperature.

**Measurements**

All microcirculatory measurements were made in a microcirculation room, at constant temperature (21°C–22°C) before 10 AM to avoid the effect of standing (particularly on edema and swelling) and after 30 minutes of acclimatization in a resting, supine position (9–12).

Laser Doppler flowmetry (LDF) resting flux (RF)—namely, the skin flux in the supine resting position—capillary filtration (measured as the rate of ankle swelling [RAS] by strain gauge plethysmography) were measured at inclusion and after 4 and 8 weeks of treatment.

**Strain-Gauge-Derived Rate of Ankle Swelling**

The RAS quantifies capillary filtration at the ankle (or foot, according to the position of the strain gauge). While the patient is resting supine
after 30 minutes, a strain-gauge is applied at the ankle level and the relationship between the strain gauge and the volume/section of the limb are calibrated (9–11). The strain gauge is placed at the minimum circumference of the ankle, just proximal to the medial malleolus. The patients is then asked to move to a standing position sup-porting the weight on the opposite leg and just touching the floor with the leg under examina -tion. The increase in volume (corresponding to the increase in section measured by the strain gauge) is then recorded for 10 minutes.

Generally, the first phase (3–4 minutes) is as -sociated with an increase in volume due to ve -nous filling (in venous patients the filling hap-pens mainly from the proximal to the distal level due to venous reflux).

The second phase is associated with venous stretching (3–4 minutes). After a period from 7 to 9 minutes, a steady-state with a very limited increase in volume is reached. The tangent to the volume increase curve measured between 7 and 10 minutes is considered to be mainly due to capillary filtration (passage of fluid, mainly water, from the intravascular to the extravascu-lar components). Reversing the position of the patient to the supine position and elevating the leg, the first components of venous volume can be eliminated in seconds (venous filling and stretching) while the small quantity of fluid passed into the interstitial fluid remains in the extravascular compartment and its volume varia-tion remains visible. In this study, in all pa-tients the leg with more severe degree of CVI was studied.

**Laser Doppler**

TSI-Vasamedics laser Doppler flowmeters (TSI, St Paul, Minnesota, USA) (9) were used to measure skin flux at the internal perimalleolar region, usually the area mostly affected by venous hypertension and microangiopathy and often a frequent localization of ulcerations in patients with CVH (12). All microcirculatory meth-ods used were performed according to the meth-ods and procedures described in detail in previ-ous publications (13–19). Measurements were only performed if all the components of the skin were intact.

A composite, analogue clinical score based on signs and symptoms (edema, pain, restless limbs, subjective swelling, skin alterations/redness) and ranging between 1 and 10 was recorded by pa-tients—after careful briefing and teaching them its meaning—at inclusion and after 4 and 8 weeks of treatment by marking on an analogue scale line the level of discomfort (Fig. 1).

Resting flux (RF) was defined as the flux at rest (1 minute of continuous recording after 20 min-utes of stabilization in resting, supine position).

A separate evaluation of edema was made by the observing physician considering a value of 0 when no edema was present and 10 when se-vere, pitting, edema was clearly visible (i.e. the value of 5-6 was associated with moderate edema without clinical signs and symptoms).

Statistical analysis was performed with the Mann-Whitney U-test. The number of patients to be included into the treatment group was cal-culated as a group of at least 10 patients needed to detect significant variations in the microcircula-
At inclusion, all included patients had signs and symptoms of severe CVI (AVP > 55 mm Hg). The duration of the disease—from the first recorded symptoms—was, on average, 5.7 (2.1) in the lower (150 mg) Pycnogenol group and 5.4 (2.0) in the Daflon group I in the first comparative study.

The duration of disease in the group treated with the higher dose (300 mg Pycnogenol) was 10 (2.1) years and 10 (2.0) years in the Daflon group II in the second comparative study.

Corresponding to the longer duration of the disease, the patients treated with the higher dose of Pycnogenol and in the comparative second Daflon group had more severe signs/symptoms of CVI at enrollment (Table 2) in comparison to the patients treated with 150 mg Pycnogenol and Daflon in the first comparative group.

The respective comparative groups (first and second study) did not differ in the intensity of symptoms/signs of CVI at inclusion (Table 2).

At the end of the treatment period of 8 weeks, a clear advantage was found for the Pycnogenol groups (Table 3) considering both signs/symptoms and microcirculatory parameters.

All microcirculatory parameters indicated a significantly larger (p < .05) improvement of CVI produced by Pycnogenol in comparison with the Daflon treatment groups (Tables 3 and 4) both in the lower dose and in the higher dose groups.

The improvement in microcirculation with Pycnogenol treatment became clear for both groups of patients considering the pO2 increase (p < .05) and that pCO2 was lowered considerably (p < .05) whereas these parameters showed only little improvement under Daflon.

Consequently, edema formation, resting flux, and rate of ankle swelling were reduced, on average, twice as much by Pycnogenol in comparison with Daflon (Tables 3 and 4).

After 4 weeks of treatment (Table 3) with 150 mg Pycnogenol, all microcirculatory parameters were improved significantly (p < .05), whereas

### RESULTS

All patients included in the treatment groups completed the study; there were no dropouts after 8 weeks of treatment.

#### TABLE 2. Signs/Symptoms and Microcirculatory Parameters of CVI at Enrollment

<table>
<thead>
<tr>
<th>Score composition</th>
<th>Score</th>
<th>RF</th>
<th>RAS</th>
<th>ASLS</th>
<th>Edema</th>
<th>pO2</th>
<th>pCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>0-2</td>
<td>3.21</td>
<td>2.38</td>
<td>8.30</td>
<td>8.90</td>
<td>46.4</td>
<td>32.1</td>
</tr>
<tr>
<td>Pain</td>
<td>0-2</td>
<td>3.23</td>
<td>2.36</td>
<td>8.32</td>
<td>8.52</td>
<td>46.1</td>
<td>31.2</td>
</tr>
<tr>
<td>Restless limbs</td>
<td>0-2</td>
<td>3.4</td>
<td>2.43</td>
<td>9.1</td>
<td>43</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td>Subjective feeling of swelling</td>
<td>0-2</td>
<td>3.43</td>
<td>2.36</td>
<td>8.92</td>
<td>44</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Skin alterations / reddening</td>
<td>0-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 1.** Visual analogue scale.
### TABLE 3. Change of CVI Symptoms (means and SD) and Microcirculation Parameters After Treatment for 4 and 8 Weeks With 150-mg Pycnogenol and 1000-mg Daflon

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>Change as percentage after 8 weeks vs start</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pycnogenol RF</td>
<td>Daflon</td>
<td>Pycnogenol RAS</td>
<td>Daflon</td>
</tr>
<tr>
<td>RF</td>
<td>3.21(0.1)</td>
<td>3.23(0.1)</td>
<td>2.1(0.11)*</td>
<td>2.8(0.1)</td>
</tr>
<tr>
<td>8</td>
<td>2.1(0.01)*</td>
<td>1.9(0.08)*</td>
<td>1.9(0.08)*</td>
<td>2.6(0.12)**</td>
</tr>
<tr>
<td></td>
<td>32.1(2)</td>
<td>32.1(2)</td>
<td>29.1(2.3)*</td>
<td>29.1(2.3)*</td>
</tr>
<tr>
<td></td>
<td>32.1(2)</td>
<td>32.1(2)</td>
<td>29.1(2.3)*</td>
<td>29.1(2.3)*</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>Change as percentage after 8 weeks vs start</td>
</tr>
<tr>
<td></td>
<td>Pycnogenol RF</td>
<td>Daflon</td>
<td>Pycnogenol RAS</td>
<td>Daflon</td>
</tr>
<tr>
<td>RF</td>
<td>-41 %</td>
<td>-20 %</td>
<td>-20 %</td>
<td>-20 %</td>
</tr>
<tr>
<td>8</td>
<td>-60 %</td>
<td>-36 %</td>
<td>-36 %</td>
<td>-36 %</td>
</tr>
<tr>
<td></td>
<td>16 %</td>
<td>-32 %</td>
<td>-32 %</td>
<td>-32 %</td>
</tr>
<tr>
<td></td>
<td>15 %</td>
<td>-12 %</td>
<td>-12 %</td>
<td>-12 %</td>
</tr>
<tr>
<td></td>
<td>0.9 %</td>
<td>-0.9 %</td>
<td>-0.9 %</td>
<td>-0.9 %</td>
</tr>
</tbody>
</table>

At 8 weeks, a clear advantage was observed for the Pycnogenol groups considering both signs/symptoms and microcirculatory parameters. All microcirculatory parameters indicated a significantly larger (p<0.05) improvement of CVI produced by Pycnogenol in comparison with the Daflon treatment groups both in the lower dose and in the higher dose groups.

| RF = resting flux; RAS = rate of ankle swelling; ASLS = analogue scale line score; EDEMA = scale 0-10. Difference before-after: *p < .05; **p < .001. #Difference between treatment groups (p < .05). |

### TABLE 4. Change of CVI Symptoms (means and SD) After Treatment With 300-mg Pycnogenol

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Groups Data</th>
<th>Start</th>
<th>8 weeks</th>
<th>Percentage Variation in Comparison with Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pycnogenol RF</td>
<td>3.4(0.1)</td>
<td>2.1(0.01)*</td>
<td>38 %</td>
</tr>
<tr>
<td></td>
<td>Daflon</td>
<td>3.43(0.1)</td>
<td>2.9(0.08)**</td>
<td>-15 %</td>
</tr>
<tr>
<td></td>
<td>Pycnogenol RAS</td>
<td>2.43(0.21)</td>
<td>1.7(0.1)*</td>
<td>-30 %</td>
</tr>
<tr>
<td></td>
<td>Daflon</td>
<td>2.36(0.18)</td>
<td>2.0(0.12)**</td>
<td>-12 %</td>
</tr>
<tr>
<td></td>
<td>Pycnogenol EDEMA</td>
<td>9.1(1.7)</td>
<td>3.2(2)*</td>
<td>-65 %</td>
</tr>
<tr>
<td></td>
<td>Daflon</td>
<td>8.92(2)</td>
<td>5.76(1)**</td>
<td>-20 %</td>
</tr>
<tr>
<td></td>
<td>Pycnogenol PO2</td>
<td>43(3)</td>
<td>49(3)*</td>
<td>+13 %</td>
</tr>
<tr>
<td></td>
<td>Daflon</td>
<td>44.14(1)</td>
<td>45.2(4)*</td>
<td>+3 %</td>
</tr>
<tr>
<td></td>
<td>Pycnogenol PCO2</td>
<td>32(2)</td>
<td>27(1)*</td>
<td>-16 %</td>
</tr>
<tr>
<td></td>
<td>Daflon</td>
<td>32.1(2)</td>
<td>31.1(1)*</td>
<td>-3 %</td>
</tr>
</tbody>
</table>

| RF = resting flux; RAS = rate of ankle swelling; ASLS = analogue scale line score. Difference before-after: *p < .05; **p < .001. #Difference between treatment groups (p < .05). |
in the comparative group treated with Daflon the improvement was smaller, not significant for most parameters.

Only the improvement of the symptom score (lower dose of Pycnogenol) reached levels of significance (p < .05).

The comparison of the effects observed with the two doses of Pycnogenol in comparison to effects obtained with Daflon (Table 5) shows that the higher dose of 300 mg was generally more effective in the reduction of edema than the lower dose (Table 5 and Fig. 2).

Other parameters showed no precise dose-dependent effect but it must be considered that the higher dose was used in patients with more severe (long-lasting) and complex disease.

Treatments were well tolerated in all groups and no side effects due to treatment were reported.

TABLE 5. Change of Treatment Parameters for Pycnogenol 150 mg and 300 mg versus Daflon 1000 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>150 mg Pycnogenol</th>
<th>Difference (%)</th>
<th>300 mg Pycnogenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting flux</td>
<td>-21.5</td>
<td>-22</td>
<td></td>
</tr>
<tr>
<td>Rate of ankle swelling</td>
<td>-16.7</td>
<td>-18</td>
<td></td>
</tr>
<tr>
<td>Symptom score</td>
<td>-23.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>-32</td>
<td>-50</td>
<td></td>
</tr>
<tr>
<td>$pO_2$</td>
<td>+13</td>
<td>+10</td>
<td></td>
</tr>
<tr>
<td>$pCO_2$</td>
<td>-12</td>
<td>-13</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 2. Percent ‘advantage’ variation in treatment parameters for Pycnogenol 150 mg and 300 mg versus Daflon 1000 mg.
DISCUSSION

CVI is often the consequence of post-thrombotic damage to the deep venous system (some 55% of patients) (1) or derives from untreated primary varicose veins and incompetence of perforator veins (43%) associated with chronic venous hypertension causing a well defined venous hypertensive microangiopathy (VHM) (1,11–20).

These chronic alterations in venous pressure and the progressive changes in major veins associated to incompetence of the superficial and or deep veins or, to deep venous obstruction, in time, cause venous microangiopathy. The most important factor associated with the development of microvascular alterations is the continuous elevation in venous pressure particularly when the patient is standing.

Venous stasis due to reduced mobility chronically increases pressure in the capillary system even in patients with mild venous disease and produce VHM and ulcers. Repeated venous pressure peaks provoked by muscle contraction when the venous system is chronically incompetent (for insufficient deep or perforating and/or superficial veins) overloads the distal capillary system at the venous end, eventually leading to skin necrosis and ulcerations (9–16). The control of venous pressure and the control of edema and microcirculatory parameters are the keys to control the pathologic microcirculatory changes in CVI. Alterations in skin flux and other microcirculatory dynamic parameters are important, quantitative measurements in the evaluation of venous microangiopathy, particularly those associated with the development of edema. The quantitative evaluation of capillary filtration is relatively complex but very effective in defining the degree of venous microangiopathy and its changes in time with treatment as an increased capillary filtration, clinically present as edema, is usually the most important, often the single, initial sign present in CVI (1–6).

This independent study confirms that oral treatment with Pycnogenol is very effective and fast in improving the microcirculation, signs, and symptoms in patients with CVI and venous microangiopathy characterized by high skin flux and increased RAS and edema.

The clinical comparison with Daflon shows a faster onset of action and 100% higher efficacy, despite the fact that the dose of Pycnogenol was 15% to 30% of the dose of Daflon.

The outcome of this comparative study is in line with the results of previous clinical trials demonstrating a higher efficacy of Pycnogenol compared to a higher dose of horse extract (25) and to troxerutine, which, ideally, could be replaced favorably in part by Pycnogenol in a new combination product (26).

Pycnogenol is safe and very well tolerated. New applications (such as prevention of flight edema and microangiopathy [27]) are important indications both for normal subjects prone to edema and for patients with venous disease.

Daflon has been studied by our group in several clinical GCP studies (29,30). In one study, laser Doppler and transcutaneous oximetry were used in patients with CVI. Results indicated a limited efficacy of the product, only in selected patients (29). Another study (30) indicated (in selected conditions and patients) a limited effect on capillary filtration and ankle edema in patients with venous hypertension.

A recent study on the clinical and hemodynamic outcomes in patients with chronic venous insufficiency after oral micronized flavonoid (Daflon) therapy (31) had the aim of investigating the clinical efficacy of Daflon therapy in patients with mild-to-moderate chronic venous insufficiency (CVI) and to assess the changes in venous hemodynamics by air plethysmography (APG). No changes in venous hemodynamics were detected by APG, suggesting that Daflon mainly acts by modifying the microcirculation and therefore changes are not detected by APG. In this study is suggested that Daflon would be useful for symptomatic relief in patients with functional venous insufficiency who do not have clinical varicose veins but suffer from symptoms of venous insufficiency.

However results from a GCP trial from our group (32) indicated that the effects of 1000 mg of Daflon on the microcirculation may be only minimal.

The association diosmin and hesperidin (Daflon) is a combination of diosmin 450 mg and flavonoids (expressed as hesperidin, 50 mg) in 500-mg tablets. It has been used in several clinical trials to fight symptoms of CVI (32,33). Some 12 comparable preparation of this combination product are available (33). In venous hypertensive microangiopathy (34) the efficacy of different flavonoids is partially dose-dependent (1,34). Recent dose-ranging studies in CVI indicate that 1000 mg of Daflon may be too low a dose to have important microcirculatory effects (35) and therefore explains the higher level of efficacy of Pycnogenol in this clinical condition.

In conclusion, the study confirms a high clinical efficacy of Pycnogenol in treating CVI and venous microangiopathy in a short time without unwanted effects.
REFERENCES


