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A Randomised Controlled Trial of Micronised Purified Flavonoid Fraction vs Placebo in Patients with Chronic Venous Disease

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Objective: *to evaluate the efficacy of a micronised purified flavonoid fraction (MPFF) in the treatment of chronic venous disease (CVD).*
Design: *prospective double blind, randomised, control study.*
Patients and methods: *one hundred and one patients with symptomatic CVD were randomly allocated to treatment for 60 days with either MPFF (51 patients) or placebo (50 patients) 500 mg twice daily. There were 28 men and 73 women, aged 22–65 years (mean age 48 years). No difference regarding age, gender, clinical class or duration of symptoms was recorded between the treatment and placebo groups. A global score for evaluation of symptoms was used. Patients were investigated with plethysmography (foot-volumetry) and duplex-ultrasonography before and after the treatment period. For statistical comparison Cochran-Mantel-Haenszel test, two-sided Student* t*-test and covariance analysis were used and* $p<0.05$ *was regarded significant.*
Results: *improvement of the global score of symptoms was reported by 21 patients in the MPFF group and by 16 in the placebo group (N.S.). For the whole groups, no significant differences were recorded before and after treatment regarding foot-volumetric or ultrasonographic parameters. On the other hand, in patients with edema (20 in the MPFF group, 23 in the placebo group) ultrasonographic reflux time was significantly reduced for those in the treatment group (*$p=0.03$*). This finding did not correlate to clinical symptoms.*
Conclusion: *in this study, MPFF did not change the symptoms of CVD, except night cramps. A secondary finding was reduced reflux times in patients with oedema, although no ultrasonographic or foot-volumetric parameters changed significantly for the whole group. The role of MPFF in treatment of patients with CVD needs to be further analysed in a large population.*

Key Words: Chronic venous disease; Pharmacological treatment; Micronised purified flavonoid fraction.

Introduction

Pharmacological treatment for chronic venous disease (CVD) is frequently used in many countries, though in Scandinavia drugs are hardly ever prescribed for CVD. Studies have shown beneficial effects of a micronised purified flavonoid fraction (MPFF) in patients with a malfunction in the "venolymphatic circulation".[1–3] In these studies most of the patients had "functional venous insufficiency" and 48%, 58% and 100% of included patients respectively had no objective signs of CVD. Utilising strain gauge plethysmography, some beneficial effects of MPFF have been observed on venous parameters, decreased venous capacity, decreased venous distensibility and lowered venous outflow time compared to placebo.[3] An increased venous tone has also been observed in normal legs.[4] It has been concluded that MPFF is of benefit to patients with chronic venous insufficiency.[5] MPFF has also been shown to decrease the level of soluble plasma markers of endothelial activation in patients with CVD.[6] Even a beneficial effect on ulcer healing has been noted.[7] Other effects that have been attributed to MPFF are inhibition of the prostaglandin synthesis, protection against free radicals, activation of the complement system and increased lymphatic drainage.[8] Based on the beneficial effects of MPFF on the microcirculation it was found valuable to perform a placebo controlled trial of MPFF in an unselected group of patients suffering CVD in Sweden. The objectives were to find out a possible correlation between clinical outcome and change of foot volumetric and duplex parameters, under the hypothesis that MPFF reduces symptom of CVD and improves venous function.

Patients and Methods

All patients referred to Lund University Hospital for surgical treatment of CVD were investigated with

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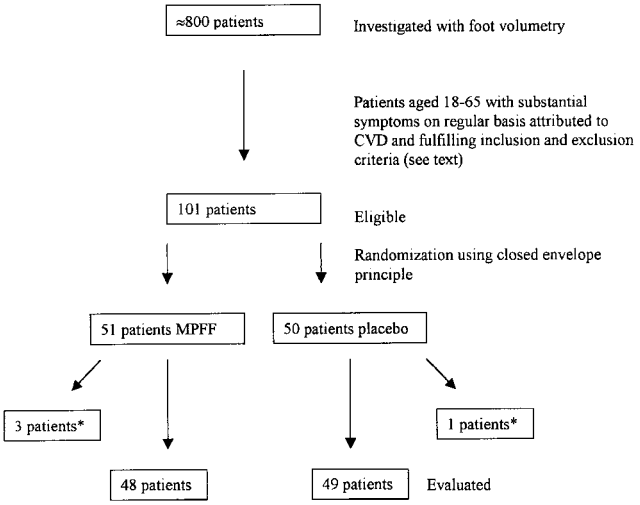

Fig. 1. Description of the study population.

duplex-ultrasonography and plethysmograpy (foot-volumetry) during the inclusion period that lasted for 20 months from 13 January 1997 to 18 October 1998. The completion date of the study with follow up on all patients was 18 December 1998. Over 800 patients were investigated during this period and those that had substantial symptoms, with duplex-ultrasound verified reflux, and fulfilling inclusion criteria, were invited to participate in the study (Fig. 1). The inclusion criteria were an age between 18–65 years and symptoms from the lower leg attributable to venous insufficiency. Exclusion criteria were diabetes, inflammatory disease, heart disease, renal disease, liver disease or peripheral arterial disease. Patients with potential allergic reactions to venoactive drugs, patients' currently taking anti-inflammatory drugs (steroids, NSAID) or diuretics were also excluded. In cases with symptoms from both legs only the leg with the most severe symptoms was included.

After informed consent, patients were randomised in a blinded fashion (sealed envelope principle) to treatment with MPFF (Daflon® 500 mg, containing 90% diosmin and 10% flavonoids expressed as hesperidin; IRIS, 92415, Courbevoie Cedex, France) or placebo b.i.d. Information was gathered about the family history of venous disease, time since occurrence of symptoms, former surgical or medical treatment, smoking and drinking habits. The following symptoms were analysed, heaviness, tiredness, ankle swelling, pain and night cramps and the patients were asked to give each symptom a score between 0 and 3, where 0 = none, 1 = mild, 2 = moderate, 3 = severe. Side effects were recorded in a similar way using a score from 0 to 3. Each patient was examined and classified according to the CEAP classification.[9]

As both subjective clinical and objective parameters were included it was not possible to determine *a priori* any expected difference between the outcome for patients on placebo and those on active treatment, respectively. One hundred and one patients with symptomatic CVD were randomly allocated to treatment for 60 days with either MPFF (51 patients) or placebo (50 patients) twice daily. There were 28 men and 73 women, aged 22–65 years (mean age 48 years). No difference regarding age, gender or duration of symptoms was recorded between the treatment and placebo groups. Sixty-nine percent of the patients had a family history of venous disorders (Table 1). The clinical class was comparable between the groups with most patients belonging to C2 (Fig. 2).

Foot-volumetry[10] was performed in the standing position and patients were asked to perform 20 knee-bends during a 40-s period. Expelled venous volume as well as refilling rate after exercise was calculated. The duplex investigation was performed supine, sitting and 60° vertical to detect venous obstruction and reflux at the femoral, popliteal and posterior tibial vein as well as in the long and short saphenous veins respectively (six levels). Pneumatic cuff with automatic inflation/release was used to evaluate the reflux time. A reflux time >0.5 s was considered pathological. After a treatment period of 60 days, clinical examination, duplex-ultrasound and foot-volumetry were repeated and the patients were asked about their symptoms as above, their overall opinion of the treatment and possible side effects. A single vascular surgeon was seeing all patients at both visits.

The Lund University Ethical Committee approved the study. Results were compared between groups using Cochran-Mantel-Haenszel test for categorical variables and two-sided Student's *t*-test or one-way analysis of covariance for continuous variables. A p-value <0.05 was regarded significant.

Results

Four patients withdrew, one in each group because of nausea, one in the placebo group who got pregnant and one in the MPFF group for reasons unrelated to the therapy. Of 97 patients that fulfilled the treatment 48 were in the MPFF group and 49 in the placebo group. Mild side effects were reported by 12% of the MPFF group compared to 4% in the placebo group. Patients overall opinion of the treatment was excellent or good in 40% of the MPFF group compared to 26% in the placebo group, none or worse in 37% of the MPFF group and 44% of the placebo group.

Table 1. Patients' characteristics.

	MPFF ($n=51$)	Placebo ($n=50$)
Mean age (range) (years)	48 (22–65)	48 (31–63)
Male/Female	12/39	16/34
Family history of CVD	72%	66%
Duration of symptoms	10 years	10 years
Mean, (range)	(5 months–45 years)	(3 months–38 years)

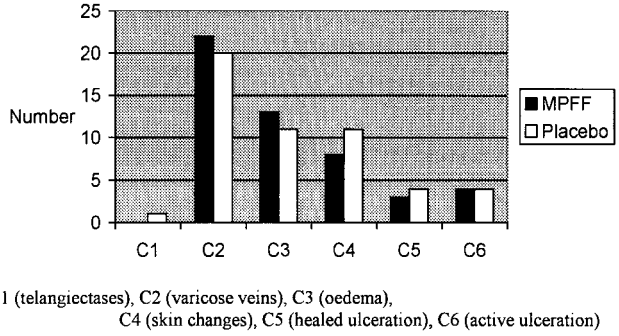

Fig. 2. Clinical class at inclusion (CEAP classification).

Table 2. Foot volumetric changes after 60 days treatment period. Mean (S.D.).

	MPFF	Placebo	
Foot volume*	+11.9 (43.4)	+4.4 (29.2)	(N.S)
EV rel.†	+0.017 (0.336)	+0.118 (0.333)	(N.S)
Q‡	−0.250 (2.394)	−0.003 (1.847)	(N.S)

* Foot volume in ml.
† Expelled volume related to foot volume in ml/100 ml.
‡ Refilling rate in ml/min × 100 ml.

Improvement of the global score of symptoms was reported by 21 patients in the MPFF group and by 16 in the placebo group. (N.S.) Night cramps were significantly reduced in patients after active treatment ($p=0.03$), with all other symptoms (heaviness, tiredness, pain and ankle swelling) remaining unchanged in both groups. For the whole groups, no significant differences were recorded before and after treatment regarding foot-volumetric or ultrasonographic parameters. Neither foot volume nor expelled volume related to foot volume changed significantly in any of the groups (Table 2).

A numerical reduction in reflux time was noted for the entire MPFF group although this reduction was not significant compared to placebo. (N.S.) In patients with oedema (20 in the MPFF group, 23 in the placebo group) ultrasonographic reflux time was significantly reduced for patients in the treatment group ($p=0.03$) (Table 3). This finding did not correlate to clinical symptoms.

Table 3. Ultrasonographic reflux time (s) in patients with oedema at inclusion. Value as mean (S.D.) (sum on six levels).

	MPFF ($n=20$)	Placebo ($n=23$)
Inclusion visit	4.34 (2.74)	5.26 (2.12)
After 60 days	3.66 (1.84)	5.46 (2.62)*

* $p=0.03$.

Discussion

A number of drugs with proposed venoactive properties are available. The Task Force on Chronic Venous Disorders of the lower leg pointed out that most of the trials on venoactive drugs were performed during the 1960s or 1970s and they rarely comply with current scientific standards for clinical trials.[11] The positive effects of venoactive drugs have mainly been a reduction of subjective symptoms and oedema and most of the studies have included patients representing such problems, and not those with an objectively proven CVD. Rutosides have been shown to improve the subjective symptom of swelling and relieve cramps but otherwise with no effect on symptoms when compared to placebo.[12] Other studies have not been able to confirm the effect of rutosides on the subjective symptom of swelling.[13,14] Calcium dobesilate[15] and dihydroergocristine[16] have been shown to relieve night cramps, pain and aching more effectively than placebo. MPFF has been shown to reduce the total score of symptoms in patients with functional and organic venous insufficiency in 71% and 66% respectively, compared to 36% and 38% respectively for the placebo group.[2] Former studies on the effect of MPFF have included patients with all kinds of symptoms from the lower leg, common for patients with CVD, but also present without CVD. It is of importance to establish the presence of CVD, if a drug treatment should be recommended based on the objective effect of the drug, not only to rely on more or less badly defined

symptoms. CVD should be defined as an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction, which may affect the superficial venous system, the deep venous system, or both and proven with objective measures.[9]

This is to the best of our knowledge the first controlled study on the effect of a venoactive drug, with an objectively verified venous insufficiency utilising duplex-ultrasound and plethysmography. Patients included in the present study had to a great extent low grade CVD (43% varicose veins only), which might explain the overall results with only a tendency to symptomatic improvement. The effects of MPFF, reduction of capillary leakage,[17] less activation of white cells[18] and increase of venous tone[4] suggest that patients with oedema and more severe CVD may benefit most from the treatment. The result achieved in patients with oedema is in line with this theory. Although only duplex-ultrasound measurements of a reduced reflux were of a significant magnitude there was a tendency to similar findings in the foot-volumetric parameters. These results suggest that medical treatment can reduce reflux, which might be an effect of venoconstriction. The clinical relevance of a shorter reflux time in patients with oedema on active treatment is, however, uncertain.

Although no significant changes were seen regarding symptoms in these patients, a higher dosage of MPFF could possibly be more effective. In a study on blood flow in the hamster cheek pouch, MPFF was able to improve the microvascular reactivity after ischaemia/reperfusion in a dose dependent way.[19] As capillary leakage and white cell activation are events that could be prevented by MPFF, further investigations are mandatory in patients with more advanced venous disease (C3–C6).

In conclusion, the present study does not give evidence for MPFF treatment for all stages of CVD. The findings in patients with oedema warrant further studies as they may benefit most of treatment with venoactive drugs.

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