The beneficial augmentative effect of micronised purified flavonoid fraction (MPFF) on the healing of leg ulcers: an open, multicentre, controlled, randomised study

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a micronised purified flavonoid fraction (MPFF) for the treatment of chronic venous insufficiency (CVI) at its most advanced phase, the leg ulcer, in addition to local therapy. The comparator was local therapy alone. Local therapy consisted of compresses of saline, 0.125% silver nitrate, or 0.1% chlorhexidine solutions twice daily, and silver sulfadiazine ointment overnight. If necessary, the surrounding skin was treated with a neutral ointment (Vaseline, zinc oxide paste, or cholesterol ointment) and washed with saline or dilute potassium permanganate solution. Compression bandages (Setopress) were applied every day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients attending dermatology outpatient clinics for the treatment of CVI in 9 polish cities (Bialystok, Gdansk, Katowice, Lublin, Lodz, Poznan, Szczecin, Warsaw and Wroclaw). The inclusion criteria specified the presence of a venous leg ulcer on one or both lower extremities, with a maximum diameter of 2 to 10 cm. Other inclusion criteria were age older than 18 years, disease duration of at least 3 months, and an ankle arm index greater than 0.9 confirmed by the Doppler flowmetry technique. Patients with congenital angiodysplasia, deep vein thrombosis within the last 15 days, and diseases of the arteries of the lower extremities were excluded from the study. Also excluded were patients with an ankle-arm index of less than 0.9, patients with diabetes, lymphoedema, connective tissue and blood diseases, and pregnant or lactating women.

Setting
The setting was dermatology outpatient clinics in 9 Polish cities (Bialystok, Gdansk, Katowice, Lublin, Lodz, Poznan, Szczecin, Warsaw and Wroclaw).

Dates to which data relate
The resource use data related to November 1998. Neither the dates for the effectiveness data nor the price year were explicitly stated.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken retrospectively on the same patient sample as that used for the effectiveness study.

**Study sample**
The authors did not report using power calculations to determine the sample size. The method of selecting the sample was not stated. One hundred and forty patients met the inclusion criteria and were randomly allocated to both groups. Seventy-one were assigned to local therapy plus MPFF and 69 to local therapy alone. In the MPFF group, 14 patients had ulcers less than 3 cm in diameter, 35 had lesions from 3 to 6 cm, and 22 had ulcers exceeding 6 cm. In the control group, these figures were 14 (<3 cm), 25 (3 - 6 cm) and 30 (>6 cm) patients, respectively.

**Study design**
This was a randomised, open, controlled study was conducted in multiple centres. The patients were allocated to one of the two treatment groups in accordance with a randomisation list developed by the Biostatistics Department of the Institut de Recherches Internationales Servier. The method of randomisation was simple. The researcher, doctor and patients all knew the treatment group. The follow-up of the study was 6 months.

**Analysis of effectiveness**
It was not stated whether the analysis of the clinical study was conducted on the basis of intention to treat or treatment completers only. The primary health outcomes considered were the percentage of patients whose ulcers healed completely, the mean reduction in ulcer size, and a 4-item table on severity of symptoms. Clinical parameters (age, gender, weight, body mass index, number of years since first ulcer, relapses, mean ulcer diameter and duration of recent ulcer) of patients included in the study were included, although no adjustment for confounding factors was reported.

**Effectiveness results**
The percentage of patients whose ulcers healed was higher in the MPFF (46.5%) group than in the control group (27.5%), (p<0.05). The odds ratio was 2.3 (95% confidence interval, CI: 1.1 - 4.6).

Ulcers of less than 3 cm in diameter were cured in 71% of the patients in the MPFF group and in 50% of those in the control group. Ulcers of between 3 and 6 cm in diameter were cured in 60% (MPFF group) and 32% (control group) of the patients, respectively, (p<0.05).

The mean reduction in ulcer size was greater in patients treated with MPPF (80%) than in the control group (65%), (p<0.05). The mean reduction of discomfort was also higher in the MPFF group, (p<0.05).

**Clinical conclusions**
The study showed that MPFF significantly improved the cure rate in patients with CVI.

**Measure of benefits used in the economic analysis**
The measure of benefits used was the number of ulcers healed.

**Direct costs**
The quantities and the costs were reported separately. Discounting was not relevant since the duration of follow-up was less than one year. The costs were those of the health service. They included direct medical costs, drugs and dressings, hospital and laboratory tests, Doppler examinations, doctors’ consultations, nursing, and adverse events (although these were not included in the economic analysis as they were reported to be similar in both groups). Market prices (e.g. drugs, dressings, ointments), data from the financial department of the hospital (cost per patient per day), and specialist consultations were used to value resource use. The price year was 1998.
Statistical analysis of costs
It was unclear from the study whether the statistical analysis to compare the two groups included costs or was limited to effectiveness data alone.

Indirect Costs
The indirect costs were out of the scope of this study.

Currency
Polish zloty (PLN). The exchange rate used was PLN 4.0340 = Euro 1.00.

Sensitivity analysis
The authors investigated variability in the data. A sensitivity analysis on those items of resource use that seemed to be disputable, such as the cost of a patient-day of hospital treatment, was carried out. The type of analysis used and the method used to select the ranges were not stated.

Estimated benefits used in the economic analysis
The percentage of patients with full healing of their ulceration was 46.5% in the MPFF group and 27.5% in the control group, (p<0.05). The odds ratio was 2.3 (95% CI: 1.1 - 4.6). The difference, 0.19, was used as the incremental effectiveness in the incremental cost-effectiveness ratio (see Synthesis of Costs and Benefits).

Cost results
The total cost per patient was PLN 1,992.20 (Euro 476.49) in the MPFF group and PLN 2,079.27 (Euro 515.44) in the control group.

Synthesis of costs and benefits
The incremental cost-effectiveness ratio of PLN compared with the control group was Euro 849 per unit of effectiveness.

Authors' conclusions
The main conclusion of the pharmacoeconomic study was that, compared with local therapy, a micronised purified flavonoid fraction (MPFF) is cost-effective for treating the leg ulcers of patients with chronic venous insufficiency (CVI).

CRD COMMENTARY - Selection of comparators
Although no explicit justification for the choice of the comparator was provided, therapy without MPFF appears to have represented standard practice in the majority of clinics in Poland.

Validity of estimate of measure of effectiveness
The authors adopted complete healing of the ulcer, mean reduction of the ulcer size, and the score of a 4-item table on severity of symptoms, as the measures of effectiveness. These appear to have been valid measures. The basis of the analysis was a randomised study, which was appropriate for the study question. Even though a selection bias (in the severity of disease in patients in the standard group) was reported, no statistical analyses were undertaken to account for it or any other confounding factors. Thus, the results obtained should be treated with some caution.

Validity of estimate of measure of benefit
No summary measure of benefit was derived so, in effect, a cost- consequences analysis was undertaken.

**Validity of estimate of costs**
The authors reported that the study had been conducted from a societal perspective, but the indirect costs were not included. The costs of adverse effects were omitted from the analysis, as they were reported to be common to both therapies. Their omission is unlikely to have affected the authors' conclusions. The quantities and the costs were reported separately and the price year was reported. This enhances the transferability of the results.

**Other issues**
The authors compared their findings with those from prior research. They stated that this piece of research conformed to the trend of good therapeutic effect with MPFF in CVI, even in patients with large ulcers. One caveat was the lack of a measure of benefits. This means it would be difficult to make comparisons with other studies and technologies necessary to help decision-makes in the allocation of resources. A second caveat was the lack of power calculations. Thus, it was difficult to ascertain whether the results obtained were due to the intervention or simply by chance.

**Implications of the study**
The results of the study supported the recommendation for supplementing standard therapy with MPFF for the treatment of patients with CVI.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; English Abstract; Female; Flavonoids /therapeutic use; Humans; Leg Ulcer /drug therapy; Male; Particle Size

**AccessionNumber**
22000001249

**Date bibliographic record published**
31/01/2005
Date abstract record published
31/01/2005