Therapeutic effect of venotonics in chronic venous insufficiency: a meta-analysis
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Authors' objectives
To evaluate the therapeutic effect of drugs administered orally in the management of primary and post-thrombotic chronic venous insufficiency.

Searching
MEDLINE was searched from 1980 to 1998 using the terms 'venous-insufficiency or varicose veins' combined with 'drug-therapy'. The Iowa Drug Information Service (IDIS) was used as a complementary database and the Cochrane Library was searched for relevant systematic reviews.

Study selection
Study designs of evaluations included in the review
Randomised, parallel or crossover, double-blind, placebo-controlled clinical trials. Studies based on short-term observations were excluded (the phrase 'short-term' was not defined in the article).

Specific interventions included in the review
Any orally administered pharmacological agent used in the management of chronic venous insufficiency. These included rutoside, flunarizine, dihydroergotamine mesylate, dihydroergotamine mesylate plus troxerutin, diosmin plus hesperidin, calcium dobesilate, sulfomucoploysaccharide, buckwheat herb extract, hidrosmin. Only studies comparing one such therapy to placebo were included. Studies that included a second active treatment or dose were excluded, even if they were also placebo-controlled. Studies of surgical, topical, intravenous or sclerosant therapies, alone or in combination with oral treatments, were also excluded.

Participants included in the review
Patients with chronic venous insufficiency. Studies of patients who were pregnant or receiving oestrogen therapy were excluded.

Outcomes assessed in the review
A wide range of subjective and objective outcome variables were included in the review, e.g. heaviness of legs, pain, oedema, cramps, paraesthesia, pruritus. Studies specifically measuring the healing of leg ulcers as an outcome were excluded from this review.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The quality of the primary studies was rated according to a scale that awarded points for study design (8 items), results and data analysis (4 items) and general aspects (5 items). The score did not have ratings for randomisation or blinding, as only double-blind randomised controlled trials (RCTs) had been selected. This assessment was performed by both reviewers independently. The reviewers were blinded to the author, title and publication journal of each article considered.

Data extraction
The data extraction was performed by both reviewers independently. The reviewers were blinded to the author, title and publication journal of each article considered. The categories of data extracted were: centre; self-citation of authors in bibliography and context of citation; precise stating of study objectives; type of study design; dose studied; baseline
characteristics of participants; selection criteria for patients; randomisation procedure; informed consent; pretrial washout; washout duration; treatment regimen; galenic preparation; treatment duration; trial duration; if use of elastic stockings was to be avoided; simultaneous treatment control; results for evaluation of clinical symptoms after at least 4 weeks of follow-up; statistical tests used; sample size calculation; withdrawals and intention to treat analysis; adverse reactions.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. For the subjective variables, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. For the objective variables, because of the wide range of measures used, an analysis based on the exact p-values rather than effect size was used (see Other Publications of Related Interest).

How were differences between studies investigated?
A chi-squared test for heterogeneity was performed. Sensitivity analyses were performed after certain studies, for which there were concerns over methodology, were excluded.

Results of the review
Twenty-one studies were included (n=817 on active treatment).

Subjective symptom assessments.
Pain (8 trials): the pooled OR was 0.46 (95% CI: 0.33, 0.65; chi-squared=11.91, p>0.05). Following the sensitivity analysis, the pooled OR was 0.68 with an upper-limit CI of 1.07.

Heaviness of legs (9 trials): the pooled OR was 0.26 (95% CI: 0.19, 0.36; chi-squared=4.06, p>0.05).

Cramps (10 trials): the pooled OR was 0.36 (95% CI: 0.26, 0.51; chi-squared=3.45, p<0.05).

Paraesthesia (4 trials): the pooled OR was 0.38 (95% CI: 0.22, 0.65; chi-squared=0.2642, p>0.05).

Objective symptom assessments.

Limb perimeter (4 studies): pooled z=3.58; pooled p=0.0003; chi-squared=1.063 (p>0.05).

Limb volume (5 studies): chi-squared=17.76 (p=0.0013), indicating that the results were too heterogeneous to pool.

Venous capacity: pooled z=3.81; pooled p=0.001; chi-squared=1.79 (p>0.05).

Venous outflow (4 studies): pooled z=3.23; pooled p=0.0089; chi-squared=1.76 (p>0.05).

Filling time (5 studies): chi-squared=18.21 (p=0.001), indicating that the results were too heterogeneous to pool.

Transcutaneous oximetry (5 studies): chi-squared=12.40 (p=0.0061), indicating that the results were too heterogeneous to pool.

Authors’ conclusions
The present analysis permits the conclusion that oral administration of venotonics may improve the heaviness of legs in patients with chronic venous insufficiency. An increase in venous outflow was also suggested by the data obtained.

CRD commentary
This was a very good, quality systematic review addressing a pertinent question. The decision of the reviewers to pool all pharmacotherapy for this indication in a single analysis appears questionable. The inclusion and exclusion criteria for
the study were defined clearly, and the literature search was reasonably comprehensive. The selection criteria in terms of study design were strict, and in addition, the quality of studies was assessed. The details of primary studies are presented in the review and the details of the meta-analysis are well-presented. The methodology used for the subjective outcomes is more reliable than that for the objective outcomes. The problem of heterogeneity is addressed by sensitivity analyses or by not pooling heterogeneous studies. Overall, the authors’ conclusions are supported by the findings of the review; whether they can be of any practical utility is questionable given the disparate nature of the drugs included in this review.

Implications of the review for practice and research
Practice: The authors state that ‘...oral drug therapy can produce an improvement of heaviness of legs in patients with chronic venous insufficiency’.

Research: The authors state that venous outflow was apparently increased (with oral drug therapy), but suitably designed studies are necessary to confirm this finding.

Research to identify which are the most efficacious agents would also appear to be required.

Bibliographic details

Other publications of related interest

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Subject indexing assigned by CRD

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.