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Horse chestnut seed extract for chronic venous insufficiency (Review)

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[Intervention Review]

Horse chestnut seed extract for chronic venous insufficiency

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ABSTRACT

Background

Conservative therapy of chronic venous insufficiency (CVI) consists largely of compression treatment. However, this often causes discomfort and has been associated with poor compliance. Therefore, oral drug treatment is an attractive option. This is an update of a Cochrane review first published in 2002 and updated in 2004, 2006, 2008 and 2010.

Objectives

To review the efficacy and safety of oral horse chestnut seed extract (HCSE) versus placebo, or reference therapy, for the treatment of CVI.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Review Group searched their Specialised Register (last searched June 2012) and CENTRAL (Issue 5, 2012). For the previous versions of the review the authors searched AMED (inception to July 2005) and Phytobase (inception to January 2001) for randomised controlled trials (RCTs) of HCSE for CVI. Manufacturers of HCSE preparations and experts on the subject were contacted for published and unpublished material. There were no restrictions on language.

Selection criteria

RCTs comparing oral HCSE mono-preparations with placebo, or reference therapy, in people with CVI. Trials assessing HCSE as one of several active components in a combination preparation, or as a part of a combination treatment, were excluded.

Data collection and analysis

Both authors independently selected the studies and, using a standard scoring system, assessed methodological quality and extracted data. Disagreements concerning evaluation of individual trials were resolved through discussion.

Main results

Overall, there appeared to be an improvement in CVI related signs and symptoms with HCSE compared with placebo. Leg pain was assessed in seven placebo-controlled trials. Six reported a significant reduction of leg pain in the HCSE groups compared with the placebo groups, while another reported a statistically significant improvement compared with baseline. One trial suggested a weighted mean difference (WMD) of 42.4 mm (95% confidence interval (CI) 34.9 to 49.9) measured on a 100 mm visual analogue scale. Leg volume was assessed in seven placebo-controlled trials. Six trials (n = 502) suggested a WMD of 32.1ml (95% CI 13.49 to 50.72) in favour of HCSE compared with placebo. One trial indicated that HCSE may be as effective as treatment with compression stockings. Adverse events were usually mild and infrequent.

Authors' conclusions

The evidence presented suggests that HCSE is an efficacious and safe short-term treatment for CVI. However, several caveats exist and larger, definitive RCTs are required to confirm the efficacy of this treatment option.

PLAIN LANGUAGE SUMMARY

Horse chestnut seed extract for long-term or chronic venous insufficiency

Poor blood flow in the veins of the legs, known as chronic venous insufficiency, is a common health problem, particularly with ageing. It can cause leg pain, swelling (oedema), itchiness (pruritus) and tenseness as well as hardening of the skin (dermatosclerosis) and fatigue. Wearing compression stockings or socks helps but people may find them uncomfortable and do not always wear them. A seed extract of horse chestnut (Aesculus hippocastanum L.) is a herbal remedy used for venous insufficiency. Seventeen randomised controlled trials were included in the review. In all trials the extract was standardised to escin, which is the main active constituent of horse chestnut seed extract.

Overall, the trials suggested an improvement in the symptoms of leg pain, oedema and pruritus with horse chestnut seed extract when taken as capsules over two to 16 weeks. Six placebo-controlled studies (543 participants) reported a clear reduction of leg pain when the herbal extract was compared with placebo. Similar results were reported for oedema, leg volume, leg circumference and pruritis. The other studies which compared the extract with rutosides (four trials), pycnogenol (one trial) or compression stockings (two trials) reported no significant differences between the therapies for leg pain or a symptom score that included leg pain. The herbal extract was equivalent to rutosides, pycnogenol and compression on the other symptoms with the exception that it was inferior to pycnogenol on oedema.

The adverse events reported (14 trials) were mild and infrequent. They included gastrointestinal complaints, dizziness, nausea, headache and pruritus, from six studies.

BACKGROUND

Description of the condition

Chronic venous insufficiency (CVI) is one of the commonest conditions afflicting humans. About 10-15% of men and 20-25% of women present signs and symptoms consistent with the diagnosis of CVI, indicating that being female is an important risk factor, as well as age, geographical location and race (Callam 1992; Callam 1994). This condition is characterised by chronic inadequate drainage of venous blood and venous hypertension, which results in leg oedema (swelling), dermatosclerosis (hardening of the skin) and feelings of pain, fatigue and tenseness in the lower extremities (Spraycar 1995). Patients often require hospitalisation and surgery, for instance, for symptomatic varicose veins (London 2000; Rigby 2002).

Description of the intervention

Mechanical compression is the treatment of choice for this condition (Partsch 1991). However, compression therapy, for example, using compression stockings often causes discomfort and has been associated with poor compliance. Oral drug treatment is therefore an attractive option.

How the intervention might work

Horse chestnut (*Aesculus hippocastanum L.*) has traditionally been used as a herbal remedy for treating CVI (Bombardelli 1996). The seed extract of *Aesculus hippocastanum L.* (HCSE) contains escin, a triterpenic saponin, as its active component (Guillaume 1994; Lorenz 1960; Schrader 1995). Escin has been shown to inhibit the activity of hyaluronidase, an enzyme involved in proteoglycan degradation (Facino 1995). The accumulation of leucocytes (white blood cells) in CVI-affected limbs (Moyses 1987; Thomas 1988) and subsequent activation and release of such enzymes (Sarin 1993) is considered to be an important pathophysiological mechanism of CVI.

Why it is important to do this review

Regardless of the postulated mechanism of action, the most important clinical questions are whether HCSE is safe and efficacious for treating patients with CVI.

OBJECTIVES

To review the evidence from rigorous clinical trials assessing the efficacy and safety of HCSE versus placebo, or reference therapy, for the symptomatic treatment of CVI.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, controlled trials (RCTs), i.e. trials with a randomised generation of allocation sequences. Studies assessing acute effects only were excluded. No restrictions regarding the language of publication were imposed (Egger 1997).

Types of participants

Studies were included if participants were patients with CVI. Studies that did not use adequate diagnostic criteria (e.g. Widmer 1978) were excluded.

Types of interventions

Trials were included if they compared oral preparations containing HCSE as the only active component (mono-preparation) with placebo or reference therapy. Trials assessing HCSE as one of several active components in a combination preparation or as a part of a combination treatment were excluded.

Types of outcome measures

Trials using clinical outcome measures were included. Studies focusing exclusively on physiological parameters were excluded.

Primary outcomes

The primary outcome measures were CVI-related symptoms (e.g. leg pain, pruritus (itching), oedema (swelling)).

Secondary outcomes

Secondary outcomes were, leg volume and leg circumference at ankle and calf. Adverse events were assessed as reported in the included trials.

Search methods for identification of studies

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched June 2012) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 5, part of *The Cochrane Library*, www.thecochranelibrary.com. See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

For the original review Phytobase inception to January 2001 and AMED were searched using the terms listed in Appendix 2 .

Searching other resources

Manufacturers of HCSE preparations and experts on the subject were contacted and asked to contribute published and unpublished material. Furthermore, our own files were scanned. The bibliographies of the studies retrieved were searched for further trials.

Data collection and analysis

Max Pittler and Edzard Ernst independently screened and selected trials for inclusion, assessed their methodological quality and extracted data. Disagreements at any of these stages were resolved by discussion.

Selection of studies

Trials were selected according to the criteria outlined above under Criteria for considering studies for this review.

Data extraction and management

Data were extracted independently by both authors using a data extraction form. Disagreements were resolved by discussion. The following data were extracted:

1. Participant characteristics: age, gender.
2. Methods used: randomisation, double-blinding, concealment of treatment allocation, description of drop outs.
3. Interventions: oral preparations containing HCSE as the only active component (mono-preparation), compared with placebo or comparator medication(s).
4. Outcome measures: CVI-related symptoms (e.g. leg pain, pruritus, oedema), leg volume, circumference at ankle and calf, and adverse events.

Assessment of risk of bias in included studies

Methodological quality was assessed using the Jadad score (Jadad 1996) and the Cochrane risk of bias tool. The Jadad score was applied independently by both authors and disagreements were resolved by discussion. The Cochrane risk of bias tool was applied by the first author only.

Measures of treatment effect

The effect measures of choice in case of dichotomous data were odds ratio (improvement of leg pain, improvement of oedema, improvement of pruritus), in case of continuous data the mean difference (reduction of leg pain, reduction of oedema, reduction of lower leg volume, reduction of circumference at ankle, reduction of circumference at calf, improvement of symptom score, leg volume).

Unit of analysis issues

There were no special issues such as carry-over effects or period effects with the analysis of the three cross over trials included in this review.

Statistical analysis was performed using RevMan Analyses 1.0.4. It uses the inverse of the variance to assign a weight to the mean of the within-study treatment effect. For most studies, however, the information was insufficient. The Cochrane Collaboration suggests imputing the variance of the change by assuming a correlation factor between pre-intervention and post-intervention values. The variance of the change was imputed using a correlation factor of 0.4, which was then used to assign a weight to the mean of the within-study treatment effect.

Assessment of heterogeneity

The chi-square test for heterogeneity tested whether the distribution of the results was compatible with the assumption that inter-trial differences were attributable to chance variation alone.

Data synthesis

Data-pooling of continuous data was performed using the weighted mean difference; for dichotomous data the odds ratio was used. Summary estimates of the treatment effect were calculated using a random effects model.

Subgroup analysis and investigation of heterogeneity

There are no planned subgroup analyses as yet. Subgroup analyses to investigate possible heterogeneity will be performed in future if more data become available.

Sensitivity analysis

There are no planned sensitivity analyses as yet. Sensitivity analyses to test the robustness of the main analysis will be performed in future if more data become available.

RESULTS

Description of studies

Included studies

Seventeen trials met the above mentioned inclusion criteria (Cloarec 1992; Diehm 1992; Diehm 1996a; Diehm 2000; Erdlen 1989; Erler 1991; Friederich 1978; Kalbfleisch 1989; Koch 2002; Lohr 1986; Morales 1993; Neiss 1976; Pilz 1990; Rehn 1996; Rudofsky 1986; Steiner 1986; Steiner 1990a). Of these, ten were placebo-controlled; two compared HCSE against reference treatment with compression stockings and placebo (Diehm 1996a; Diehm 2000); four were controlled against reference medication with O-ß-hydroxyethyl rutosides (HR) (Erdlen 1989; Erler 1991; Kalbfleisch 1989; Rehn 1996) and one was controlled against medication with pycnogenol (Koch 2002). In all trials the extract was standardised to escin which is the main active constituent of HCSE.

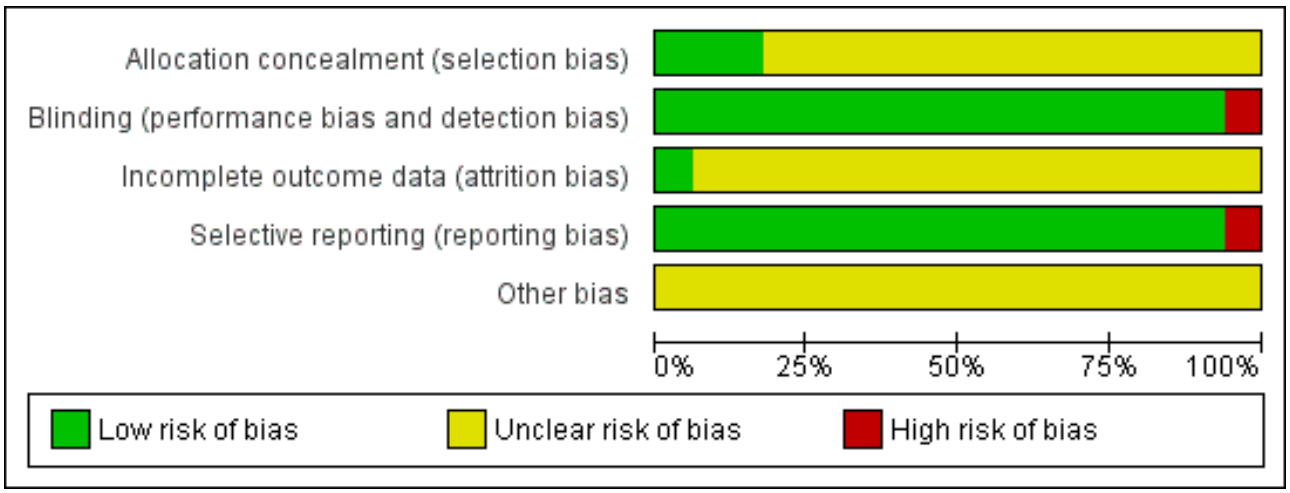
Excluded studies

Fourteen trials were excluded (Bisler 1986; Boehm 1989; Coninx 1974; Dols 1987; Dustmann 1984; Hirsch 1982; Krc¡lek 1973; Lochs 1974; Marhic 1986; Nill 1970; Neumann-Mangoldt; Paciaroni 1982; Pauschinger 1987; Zuccarelli 1986). The trial by (Pauschinger 1987;) used non-clinical outcome measures; seven tested HCSE as a component in combination preparations or combination treatments (Boehm 1989; Coninx 1974; Dols 1987; Dustmann 1984; Hirsch 1982; Neumann-Mangoldt; Zuccarelli 1986); and two focused exclusively on physiological parameters (Bisler 1986; Lochs 1974). The four additional trials identified through update searches were excluded because they used topical treatment (Marhic 1986; Paciaroni 1982), did not asses clinical outcomes (Nill 1970) or tested a combination preparation (Krc¡lek 1973).

Risk of bias in included studies

Figure 1 displays the risk of bias associated with the included studies.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Key data from the included trials, including scores for quality and allocation concealment, are presented in the Characteristics of included studies table.

Allocation

Most trials did not report on allocation concealment and it is therefore unclear to what extent bias was introduced. Only three trials (Erdlen 1989; Pilz 1990; Steiner 1986) reported adequate allocation concealment.

Blinding

Only one of the included RCTs was not double-blinded (Koch 2002). All of the included studies administered HCSE in capsules, permitting the preparation of adequate placebos. The likelihood that bias was introduced through blinding or the lack thereof is minimal.

Incomplete outcome data

In all but three studies (Friederich 1978; Steiner 1990a; Rehn 1996) it is unclear whether incomplete outcome data were addressed. It is therefore unclear to what extent bias was introduced.

Selective reporting

None of the included trials showed evidence of selective reporting and therefore it is unlikely that bias was introduced here. In the included trials, all of the pre-stated outcomes were reported.

Effects of interventions

The majority of the included studies diagnosed the patients according to the classification by Widmer (Widmer 1978). Fourteen trials reported inclusion criteria for CVI patients relating to this classification. Eighty-two percent of the participants in these trials were categorised into CVI stages I, II or I-II. Three trials, comprising 22% of the total number of participants did not refer to this classification. Overall, the included placebo-controlled trials suggested an improvement in the CVI related symptoms of leg pain, oedema and pruritus.

Leg pain

Leg pain was assessed in seven placebo-controlled trials (Cloarec 1992; Friederich 1978; Lohr 1986; Morales 1993; Neiss 1976; Rudofsky 1986; Steiner 1990a). Six studies (n = 543) reported a statistically significant reduction ($P < 0.05$) of leg pain on various measurement scales in participants treated with HCSE compared with placebo, while another reported an improvement compared with baseline (Steiner 1990a). One study (Cloarec 1992), reported adequate data which could be included within RevMan Analyses (Analysis 1.2), assessed on a 100 mm VAS, suggesting a weighted mean difference (WMD) of 42.40 mm (95% confidence interval (CI) 34.90 to 49.90). Other studies which compared HCSE with HR (Kalbfleisch 1989), pycnogenol (Koch 2002) or compression (Diehm 2000) reported no significant inter group differences for leg pain or a symptom score including leg pain.

Oedema

Oedema was assessed in six placebo-controlled trials (Cloarec 1992; Friederich 1978; Lohr 1986; Morales 1993; Neiss 1976; Steiner 1990a). Four trials (n = 461) reported a statistically significant reduction of oedema in participants treated with HCSE compared with placebo, whilst one (Steiner 1990a) reported an improvement compared with baseline. One study (Cloarec 1992) reported adequate data suggesting a WMD of 40.10 mm (95% CI 31.60 to 48.60) in favour of HCSE assessed on a 100 mm VAS. Another study (Koch 2002) reported that HCSE was inferior to pycnogenol, whereas a further trial (Diehm 2000) reported no significant differences for a score including the symptom oedema compared with compression. Oedema provocation before and after treatment with HCSE revealed oedema protective effects (Erler 1991).

Pruritus

Pruritus was assessed in eight placebo-controlled trials (Diehm 1992; Friederich 1978; Lohr 1986; Morales 1993; Neiss 1976; Rudofsky 1986; Steiner 1986; Steiner 1990a). Four trials (n = 407) suggested a statistically significant reduction of pruritus in participants treated with HCSE compared with placebo ($P < 0.05$). Two trials (Steiner 1986; Steiner 1990a) suggested a statistically significant difference in favour of HCSE compared with baseline ($P < 0.05$). Another trial (Kalbfleisch 1989), which compared HCSE with

HR, but failed to include a placebo group, seemed to corroborate these findings. A further trial (Diehm 2000) reported no significant differences for a score including the symptom pruritus compared with compression.

Leg volume

Leg volume was assessed in seven placebo-controlled trials (Diehm 1992; Diehm 1996a; Diehm 2000; Lohr 1986; Rudofsky 1986; Steiner 1986; Steiner 1990a). All of these studies used water displacement plethysmometry to measure this outcome. Meta-analysis of six trials (Diehm 1992; Diehm 1996a; Diehm 2000; Rudofsky 1986; Steiner 1986; Steiner 1990a; n = 502) suggested a WMD of 32.1ml (95% CI 13.49 to 50.72) in favour of HCSE compared with placebo (Analysis 1.6) (pooled standardised mean difference 0.34; 95% CI 0.15 to 0.52). One trial (Rehn 1996) reported findings suggesting that HCSE was equivalent to HR, and another (Diehm 1996a, n = 194) suggested that it may be as efficacious as treatment with compression stockings (WMD -2.90 ml; 95% CI -30.42 to 24.62).

Significant beneficial effects for CVI patients were reported in trials which administered HCSE standardised to 100-150 mg escin daily. Three studies, using 100 mg escin daily, reported a statistically significant reduction of mean leg volume after two weeks of treatment compared with placebo ($P < 0.01$) (Rudofsky 1986; Steiner 1986; Steiner 1990a). Persistence of treatment effects was suggested by one study (Rehn 1996). At the end of a six-week follow-up period mean leg volume was similar to post-treatment values.

Circumference

Circumference at calf and ankle was assessed in seven placebo-controlled trials (Cloarec 1992; Diehm 1992; Lohr 1986; Pilz 1990; Rudofsky 1986; Steiner 1986; Steiner 1990a). Five studies (n = 172) suggested a statistically significant reduction at the ankle, and three (n = 112) at the calf in favour of HCSE compared with placebo. At the ankle, meta-analysis of three trials (Cloarec 1992; Pilz 1990; Steiner 1986), which reported adequate data suggested a statistically significant reduction in favour of HCSE compared with placebo (WMD 4.71 mm; 95% CI 1.13 to 8.28; pooled standardised mean difference 0.60; 95% CI 0.15 to 1.05) (Analysis 1.7). At the calf, the pooled analysis of three trials (Cloarec 1992; Pilz 1990; Steiner 1986), suggested a statistically significant reduction in favour of HCSE compared with placebo (WMD 3.51 mm; 95% CI 0.58 to 6.45; pooled standardised mean difference 0.42; 95% CI -0.04 to 0.88).

Adverse events

Fourteen studies reported on adverse events. Four studies (Cloarec 1992; Diehm 1996a; Pilz 1990; Rudofsky 1986) reported that there were no treatment-related adverse events in the HCSE group. Gastrointestinal complaints, dizziness, nausea, headache and pruritus were reported as adverse events in six studies (Diehm 2000; Friederich 1978; Morales 1993; Neiss 1976; Rehn 1996; Steiner 1990a). The frequency ranged from 1 to 36% of treated patients. Four other studies (Diehm 1992; Koch 2002; Lohr 1986; Steiner 1986) reported good tolerability with HCSE.

DISCUSSION

Summary of main results

The results of our systematic review suggest, overall, that compared with placebo and reference treatment, HCSE is an effective treatment option for CVI. The adverse events reported in the reviewed trials were mild and infrequent. Thus, according to the available data the risk/benefit ratio of HCSE for the short term treatment of CVI is positive.

Overall completeness and applicability of evidence

In an attempt to locate all randomised trials of oral preparations containing HCSE, 29 trials were identified of which 17 could be included. It is noteworthy that one unpublished trial was supplied by a manufacturer of HCSE-containing preparations, while a second unpublished trial was identified in a report by another author (Diehm 2000). The search strategy for this review involved several databases including those with a focus on the European and American literature, as well as manual searching and contact with experts and manufacturers. Moreover, searching was not restricted in terms of publication language.

The conservative treatment of CVI comprises a number of other therapeutic modalities. Compression therapy improves venous return and is widely accepted as the treatment of choice (Tooke 1996). In combination with heparin, it prevents venous stasis and reduces the risk of deep vein thrombosis. O-ß-hydroxyethyl rutosides are reported to have beneficial short-term effects by reducing oedema and relieving symptoms of CVI. However, their efficacy during long-term use has yet to be established (Wadworth 1992). Ruscus extract decreases capillary filtration rate in healthy volunteers and people with CVI (Rudofsky 1991). A review has concluded that combined treatment using oedema protective agents and compression therapy improves CVI to a greater extend than either treatment alone (Diehm 1996b).

The mechanism of action involved in the observed effects when HCSE is administered may be of interest. The active component of HCSE is the saponin escin (Lorenz 1960). This has been shown to inhibit the activity of elastase and hyaluronidase *in vitro*. Both these enzymes are involved in proteoglycan degradation (proteoglycan constitutes part of the capillary endothelium and is the main component of the extravascular matrix) (Facino 1995). The accumulation of leucocytes (white blood cells) in CVI-affected limbs (Moyses 1987; Thomas 1988), and subsequent activation and release of such enzymes (Sarin 1993), is considered to be an important pathophysiological mechanism of CVI. An earlier study found increased serum activity of proteoglycan hydrolases in patients with CVI that were reduced with HCSE (Kreysel 1983). HCSE treatment may shift the equilibrium between degradation and synthesis of proteoglycans towards a net synthesis, thus preventing vascular leakage. This hypothesis has been supported by animal experiments (Enghofer 1984). Using electron microscopy, the author demonstrated a marked reduction in vascular leakage after treatment with HCSE. Uncertainty exists regarding the effects of HCSE on venous tone. *In vitro*, HCSE increases venous pressure of normal and pathologically altered veins. This is corroborated by studies in laboratory animals, which demonstrate an increase in venous pressure and venous flow after HCSE administration (Guillaume 1994). However, studies on humans have failed to replicate effects on venous capacity (Bisler 1986; Rudofsky 1986).

Quality of the evidence

All randomised double-blind trials included in this review scored at least one out of five points for methodological quality. Nonetheless, the extent of methodological rigour varied between studies. Only

three trials (Diehm 1996a; Rehn 1996; Rudofsky 1986) reported data indicating that compliance was monitored. The majority of studies suffered from a small sample size with drop-out rates ranging from zero to 19.5%.

Potential biases in the review process

Despite systematic efforts to find all studies on the subject, it is conceivable that some were not uncovered. Several forms of publication and location bias exist (Egger 1998) including the tendency for negative trials to remain unpublished (Easterbrook 1991), for positive findings to be published in English language journals (Egger 1997) and for some European journals to not be indexed in major medical databases (Nieminen 1999). There is also evidence that positive findings may be over-represented in complementary medicine journals (Ernst 1997; Schmidt 2001) and that these journals favour positive conclusions at the expense of methodological quality (Pittler 2000). Therefore, there is a possibility that treatment effects are exaggerated. Overall, we are confident that the search strategy that we used and the therefore the completeness of the evidence minimised bias. However, more trials assessing the efficacy of HCSE in larger patient samples using adequate outcome measures and systematic investigations of its safety are still required (Ernst 2001).

Agreements and disagreements with other studies or reviews

These findings update and extend the findings of previous systematic reviews (Pittler 1998; Pittler 2004; Siebert 2002). In the reviewed trials adverse events were mild and infrequent, which supports the findings of post-marketing surveillance studies (Greeske 1996; Leskow 1996) reporting pruritus, nausea, gastrointestinal complaints, headache and dizziness in 43 of 6183 patients (0.7%) treated with HCSE.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence presented suggests that HCSE is an efficacious and safe short-term treatment for CVI. However, caveats exist and more rigorous, large RCTs are required to assess the efficacy of this treatment option.

Implications for research

Future studies should be rigorously executed and reported in a uniform manner following the CONSORT statement (Moher 2001). Detailed description of randomisation and double-blinding procedures should be included in the report. More controlled clinical trials are needed, which should include larger numbers of participants and assess HCSE particularly for long-term use and as an adjunct to compression treatment.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cloarec 1992

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: none. Losses to follow up: none. Quality score = 3.
Participants	Country: France. Setting: hospital. No: 30 entered, 0 drop outs. Age: (mean) 45.5 and 47.7 years in HCSE and placebo group, respectively. Sex: males 15; females 15. Inclusion criteria: patients with functional symptoms due to CVI at least in one leg; patients with impression oedema at least in one leg. Exclusion criteria: systolic blood pressure ankle/arm > 0.9; acute or precedent (< 1 month) thrombophlebitis; leg ulcer of venous origin; cardiac, renal or orthopaedic oedema.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 4 weeks.

Cloarec 1992 *(Continued)*

Outcomes	Primary: (not explicitly stated). Secondary: (not explicitly stated). 1) circumference (mm) 2) leg pain (mm) 3) oedema (mm)
Notes	Standardised mean difference (95% CI): 1) circumference a) ankle 0.57 (-0.16 to 1.30) b) calf 0.26 (-0.46 to 0.98) 2) 3.93 (2.65 to 5.22) 3) 3.28 (2.14 to 4.43)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"In a double blind study Venostasin versus placebo was studied in 30 cases ..."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed; intention to treat analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Diehm 1992

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: block randomisation. Exclusion post randomisation: one patient. Losses to follow up: none. Quality score = 4.
Participants	Country: Germany. Setting: hospital. No: 40 entered, 1 excluded post randomisation. Age: (mean) 53 and 48 years in treatment and control groups, respectively. Sex: reported males 9; females 29.

Diehm 1992 *(Continued)*

	Inclusion criteria: CVI stage 2 according to Hach, venous flow impairment, oedema, possible trophic skin changes, venous capacity and / or venous return outside normal limits. Exclusion criteria: CVI liable to venous compression, acute venous inflammation, acute thrombosis, venous ulceration, oedema due to other conditions than CVI.
Interventions	Treatment: 1 capsule HCSE (standardised to 75 mg escin) twice daily. Control: placebo. Duration: 6 weeks.
Outcomes	Primary: leg volume (ml). Secondary: 1) circumference 2) pruritus
Notes	Standardised mean difference (95% CI): Primary: 0.30 (-0.33 to 0.94) Secondary: 1), 2) Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"The double blind nature of the trial as assured by using placebos which in terms of outer appearance and taste were identical to verum"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of further biases

Diehm 1996a

Methods	Study design: 3 parallel arms, randomised, double-blinded (for placebo and HCSE only). Method of randomisation: not reported. Exclusion post randomisation: none. Losses to follow up: not reported. Quality score = 2.
Participants	Country: Germany.

Diehm 1996a *(Continued)*

	Setting: hospital. No: 240 entered, drop outs not reported. Age: (mean) 52 years. Sex: not reported. Inclusion criteria: oedema due to CVI (confirmed by medical history, clinical findings, venous Doppler and duplex sonography. Exclusion criteria: venotherapeutic drugs within the last 6 weeks before run-in.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo or compression stockings. Duration: 12 weeks.
Outcomes	Primary: (not explicitly stated) leg volume (ml). Secondary: (not explicitly stated) circumference, symptoms .
Notes	Standardised mean difference (95% CI): Primary: HCSE versus placebo 0.49 (0.14 to 0.85) HCSE versus compression -0.03 (-0.31 to 0.25)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients were treated over a period of 12 weeks in a randomised partially blinded placebo controlled paralles study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Diehm 2000

Methods	Study design: 3 parallel arms, randomised, double-blind. Method of randomisation: not reported.

Diehm 2000 *(Continued)*

	Exclusion post randomisation: not reported. Losses to follow up: 69. Quality score = 2.
Participants	Country: Germany. Setting: unclear. No: 355 entered, drop outs 69. Age: not reported. Sex: not reported. Inclusion criteria: CVI stage II and IIIA. Exclusion criteria: venotherapeutic drugs within the last 6 weeks, patients with oedema of non-venous origin.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo or compression stockings. Duration: 16 weeks.
Outcomes	Primary: leg volume (ml). Secondary: symptom score computed from: 1) feeling of swelling 2) tiredness in the leg 3) itching 4) leg cramps 5) paraesthesia 6) plantar burning 7) unspecific complaints
Notes	Standardised mean difference (95% CI): Primary: HCSE versus placebo 0.26 (-0.03 to 0.54) HCSE versus compression 0.70 (-0.94 to 0.46) Secondary: HCSE versus compression 0.06 (-0.17 to 0.29)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study was double-blind regarding allocation to HCSE or placebo and open regarding allocation to the compression group"
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear how incomplete outcome data were addressed

Diehm 2000 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	Reported within a review article only

Erdlen 1989

Methods	Study design: 2 parallel arms, randomised double-blind. Method of randomisation: Central randomisation by company. Exclusion post randomisation: not reported. Losses to follow up: not reported. Quality score = 4.
Participants	Country: Germany. Setting: GP setting. No: 30 entered, drop outs not reported. Age: (mean) 55 years in treatment group; no data for control. Sex: males 10; females 20. Inclusion criteria: varicosis due to CVI, peripheral venous oedema. Exclusion criteria: oedema due to other conditions than CVI, vasoactive medication, compression treatment, venous ulcers.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: rutoside. Duration: 4 weeks.
Outcomes	Primary: circumference (mm). Secondary: not reported.
Notes	Standardised mean difference (95% CI): Primary: ankle 0.0 (-0.72 to 0.72)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Block randomisation was done. Random codes were kept in sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment and placebo capsules were indistinguishable in terms of outer appearance

Erdlen 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of further biases

Erler 1991

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: block randomisation. Exclusion post randomisation: not reported. Losses to follow up: not reported. Quality score = 3.
Participants	Country: Germany. Setting: hospital. No: 40 entered, drop outs not reported. Age: (mean) 55.5 and 53.9 years in treatment and control group, respectively. Sex: males 10; females 20. Inclusion criteria: oedema due to CVI. Exclusion criteria: oedema due to other conditions than CVI, vasoactive medication, compression treatment, venous ulcers.
Interventions	Treatment: 1 capsule HCSE (standardised to 75 mg escin) twice daily. Control: O-beta-hydroxyethyl rutosides (2 g daily). Duration: 8 weeks.
Outcomes	Primary: circumference before and after oedema provocation. Secondary: (not explicitly defined) symptoms (leg pain, oedema, pruritus, fatigue).
Notes	Standardised mean difference (95% CI): Primary: Not enough data provided for effect size calculation. Secondary: Not enough data provided for effect size calculation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported

Erler 1991 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Neutrally coated capsules which were indistinguishable in terms of outer appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of further biases

Friederich 1978

Methods	Study design: crossover, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: not reported. Losses to follow up: 23. Quality score = 4.
Participants	Country: Germany. Setting: hospital. No: 118 entered, 23 drop outs. Age: (mean) 48 and 47 years in men and women, respectively. Sex: males 11; females 107. Inclusion criteria: oedema, leg pain, pruritus, feeling of tenseness and fatigue. Exclusion criteria: not reported.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 20 days.
Outcomes	Primary: (not explicitly defined) symptoms 1) leg pain 2) oedema 3) pruritus Secondary: (not explicitly defined) patients' impression of effectiveness.
Notes	Standardised mean difference (95% CI): Primary: 1), 2), 3) Not enough data provided for effect size calculation. Secondary:

Friederich 1978 *(Continued)*

	Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment and placebo capsules were identical in terms of outer appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of further biases

Kalbfleisch 1989

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: none. Losses to follow up: three. Quality score = 4.
Participants	Country: Germany. Setting: GP practice. No: 33 entered, 3 drop outs. Age: "18 years and over". Sex: male and female (numbers not reported). Inclusion criteria: CVI and oedema. Exclusion criteria: cardiac and hepatic oedema, patients with kidney and liver dysfunctions, venous ulcers, vasoactive medication, NSAIDs, glucosides.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) once daily. Control: O-beta-hydroxyethyl rutosides (50 mg daily). Duration: 8 weeks.
Outcomes	Primary: (not explicitly stated) circumference (mm).

Kalbfleisch 1989 *(Continued)*

	Secondary: (not explicitly stated) 1) leg pain (mm) 2) oedema (mm) 3) pruritus
Notes	Standardised mean difference (95% CI): Primary: a) ankle 2.13 (1.20 to 3.06) b) calf 1.83 (0.95 to 2.21) Secondary: 1) 0.19 (-0.54 to 0.91) 2) -0.25 (-0.97 to 0.48) 3) Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment and placebo capsules were neutrally coated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of further biases

Koch 2002

Methods	Study design: 2 parallel arms, randomised, open. Method of randomisation: not reported. Exclusion post randomisation: one. Losses to follow up: not reported. Quality score = 1.
Participants	Country: Germany. Setting: GP practice. No: 40 entered, drop outs not reported. Age: (mean) 56 and 59 years in HCSE and pycnogenol group respectively. Sex: males 7; females 33.

Koch 2002 *(Continued)*

	Inclusion criteria: CVI. Exclusion criteria: not reported.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin twice daily). Control: pycnogenol (360 mg daily). Duration: 4 weeks.
Outcomes	Primary: (not explicitly defined) 1) Symptoms a) leg pain b) oedema c) cramps d) feeling of heaviness e) leg reddening 2) Circumference (mm). Secondary: (not explicitly defined) Serum cholesterol.
Notes	1), 2) Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	High risk	"In an open controlled comparative study 40 patients with diagnosed CVI were treated."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Lohr 1986

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: not reported. Losses to follow up: 6. Quality score = 3.
Participants	Country: Germany.

Lohr 1986 *(Continued)*

	Setting: GP practice. No: 80 entered, 6 drop outs. Age: (mean) 54 years in total patient sample. Sex: males 17; females 57. Inclusion criteria: CVI. Exclusion criteria: not reported.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 8 weeks.
Outcomes	Primary: leg volume Secondary: 1) circumference 2) leg pain 3) oedema 4) pruritus
Notes	Primary and secondary outcomes: Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was conducted randomised and double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Morales 1993

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: not reported. Losses to follow up: three.

Morales 1993 *(Continued)*

	Quality score = 3.
Participants	Country: Brazil. Setting: hospital. No: 54 entered, 3 drop outs. Age: (mean) 40 years in total patient sample. Sex: males 2; females 52. Inclusion criteria: oedema, varicosis, venous ulcers. Exclusion criteria: diabetes mellitus, oedema of other origin, peripheral arterial disease, diuretic medication.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 20 days.
Outcomes	Primary: (not explicitly defined) oedema Secondary: (not explicitly defined) 1) leg pain 2) pruritus
Notes	Primary and secondary outcomes: Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"This is a double blind randomised placebo controlled parallel study of the ise of dried horse chestnut extract (Venostasin retard) in chronic venous insufficiency of the limbs:"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	High risk	No evidence for selective reporting
Other bias	Unclear risk	No evidence of further biases

Neiss 1976

Methods	Study design: crossover, randomised, double-blind. Method of randomisation: not reported.

Neiss 1976 *(Continued)*

	Exclusion post randomisation: not reported. Losses to follow up: seven. Quality score = 3.
Participants	Country: Germany. Setting: GP practice. No: 233 entered, 7 drop outs. Age: (mean) 56 and 55 in women and men, respectively. Sex: males 29; females 197. Inclusion criteria: CVI with symptoms including oedema, leg pain, pruritus fatigue and tenseness, calf cramps. Exclusion criteria: concomitant medication or physical treatments.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 20 days.
Outcomes	Primary: (not explicitly defined) symptoms 1) leg pain 2) oedema 3) pruritus 4) feeling of fatigue and tenseness 5) calf cramps Secondary: not described.
Notes	1), 2), 3), 4), 5) Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"...the study was carried out in a double-blind design."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Pilz 1990

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: block randomisation. Exclusion post randomisation: two. Losses to follow up: none. Quality score = 4.
Participants	Country: Germany. Setting: GP practice. No: 30 entered, 2 drop outs. Age: (mean) 46 in total patient sample. Sex: males 6; females 24. Inclusion criteria: Symptoms of CVI with peripheral leg oedema. Exclusion criteria: patients under 20 and over 70 years of age, less than 2 symptoms of CVI, leg ulcers, oedema or leg pain of other origin than CVI, rheumatic diseases, concomitant medication, compression treatment.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 20 days.
Outcomes	Primary: (not explicitly stated). Secondary: (not explicitly stated).
Notes	Standardised mean difference (95% CI): Primary: circumference (mm). a) ankle 0.70 (-0.04 to 1.45) b) calf 0.86 (0.11 to 1.61) Secondary: (not explicitly stated) adverse events. none.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Block randomisation and allocation of patients to treatment and control groups was performed centrally by Klinge Pharma. The random code was stored in sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Verum and placebo were indistinguishable in terms of outer appearance and taste
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed

Pilz 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Rehn 1996

Methods	Study design: 3 parallel arms, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: not reported. Losses to follow up: 21. Quality score = 4.
Participants	Country: Germany. Setting: not reported. No: 158 entered, 21 drop outs. Age: mean 58.4 years ß-hydroxyethyl-rutosides (1 g daily) group; 62.8 years ß-hydroxyethyl-rutosides (1 to 0.5 g daily) group; 59.0 years HCSE group. Sex: all females. Inclusion criteria: uni- or bilateral CVI stage II, doppler sonographic assessment within the past 6 months. Exclusion criteria: oedema due to other conditions than CVI, over 70 years of age, current acute phlebitis or thrombosis, concomitant medication, compression treatment.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: ß-hydroxyethyl-rutosides (1 g daily) or ß-hydroxyethyl-rutosides (1 to 0.5 g daily). Duration: 12 weeks.
Outcomes	Primary: leg volume (ml). Secondary: Symptoms: tired, heavy legs (VAS (mm)).
Notes	Standardised mean difference (95% CI): Primary: HR (1g): -0.17 (-0.56 to 0.22) HR (1 to 0.5g): 0.05 (-0.38 to 0.48) Secondary: (mean, SD) 4.1, 2.9; 3.8, 2.6; 3.0, 2.2 at baseline for beta-HR 1 g, beta-HR 1 to 0.5 g and HCSE respectively. -1.5, 3.0; -1.0, 3.3; -0.2, 2.5 are the respective changes from baseline (no formal statistical analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement

Rehn 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"According to the double dummy procedure both for oxerutin film tablets and horse chestnut extract capsules identically appearing placebo tablets or capsules were used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing data were interpolated if possible or the method of last value carry forward was used."
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other biases

Rudofsky 1986

Methods	Study design: 2 parallel arms, randomised, double-blind. Method of randomisation: random number generator. Exclusion post randomisation: none. Losses to follow up: 1. Quality score = 5.
Participants	Country: Germany. Setting: hospital. No: 40 entered, 1 drop out. Age: (mean) 41 and 38 years in treatment and placebo groups, respectively. Sex: males 14, females 25. Inclusion criteria: clinical signs of CVI (e.g. varicosis, hyperpigmentation), symptoms (e.g. leg pain, pruritus), venous capacity of over 6 ml per 100 ml tissue, venous pressure (dorsum pedis) of at least 60 mmHg. Exclusion criteria: CVI stage III, acute phlebitis, oedema of other origin than CVI, concomitant medication (e.g. diuretics, vasoactive drugs).
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 4 weeks.
Outcomes	Primary: (not explicitly stated) leg volume (ml) Secondary: (not explicitly stated) 1) circumference 2) leg pain 3) pruritus

Rudofsky 1986 *(Continued)*

Notes	Standardised mean difference (95% CI): Primary: 0.46 (-0.18 to 1.10) Secondary: Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Verum and placebo capsules were indistinguishable .... Thus it was impossible for physician and patient to determine whether they received the true or placebo medication
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	There is no evidence of other biases

Steiner 1986

Methods	Study design: crossover, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: none. Losses to follow up: none. Quality score = 4.
Participants	Country: Germany. Setting: hospital. No: 20 entered, drop outs none. Age: (range) 20 to 40 years in total patient sample. Sex: all females. Inclusion criteria: CVI stage I, peripheral venous oedema. Exclusion criteria: Patients in third trimenon, CVI stages II and III, diuretics, vasoactive medication.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo.

Steiner 1986 *(Continued)*

	Duration: 2 weeks.
Outcomes	Primary: leg volume (ml) Secondary: 1) circumference (mm) 2) symptoms (e.g. pruritus).
Notes	Standardised mean difference (95% CI): Primary: 0.41 (-0.48 to 1.30) Secondary: 1) a) ankle 0.48 (-0.41 to 1.38) b) calf 0.07 (-0.81 to 0.95) 2) Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	The random code was kept in sealed envelopes (information from duplicate publication Steiner 1990b)
Blinding (performance bias and detection bias) All outcomes	Low risk	Verum and placebo capsules were indistinguishable in terms of colour and taste (information from duplicate publication Steiner 1990b)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	No evidence of other bias

Steiner 1990a

Methods	Study design: crossover, randomised, double-blind. Method of randomisation: not reported. Exclusion post randomisation: not reported. Losses to follow up: two. Quality score = 4.
Participants	Country: Germany. Setting: hospital. No: 52 entered, 2 drop outs.

Steiner 1990a *(Continued)*

	Age: (mean) not reported. Sex: all females. Inclusion criteria: over 18 years of age, varicose veins and clinically detectable oedema, CVI had to be confirmed by at least two of either Doppler sonography, plethysmography venous pressure measurements or light reflection rheography. Exclusion criteria: not described.
Interventions	Treatment: 1 capsule HCSE (standardised to 50 mg escin) twice daily. Control: placebo. Duration: 2 weeks.
Outcomes	Primary: 1) leg volume (ml) 2) circumference (mm) Secondary: symptoms: leg pain, pruritus, oedema, fatigue.
Notes	Standardised mean difference (95% CI): Primary: 1) 0.15 (-0.40 to 0.71) 2) Not enough data provided for effect size calculation. Secondary: Not enough data provided for effect size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients were given either one capsule of Venostasin retard twice daily or an identical placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear how incomplete outcome data were addressed. Drop outs are described: "Of the 52 patients who were entered two patients discontinued the study; one had to undergo an operation and the other was lost to follow-up"
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	There is no evidence of other biases

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bisler 1986	Used non-clinical outcome measures.
Boehm 1989	HCSE applied as part of a combination preparation.

Study	Reason for exclusion
Coninx 1974	HCSE applied as part of a combination preparation.
Dols 1987	HCSE applied as part of a combination preparation.
Dustmann 1984	HCSE applied as part of a combination preparation.
Hirsch 1982	HCSE applied as part of a combination preparation.
Krc¡lek 1973	HCSE applied as part of a combination preparation.
Lochs 1974	Trial performed on healthy volunteers, not people with CVI.
Marhic 1986	Used cream, not oral preparation.
Neumann-Mangoldt	HCSE applied as part of a combination preparation.
Nill 1970	Used non-clinical outcome measures.
Paciaroni 1982	Used cream, not oral preparation.
Pauschinger 1987	Used non-clinical outcome measures.
Zuccarelli 1986	HCSE applied as part of a combination preparation.

DATA AND ANALYSES

Comparison 1. HCSE versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of leg pain (responder ratio)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2 Reduction of leg pain (100 mm VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Reduction of oedema (100 mm VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Improvement of oedema (responder ratio)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
5 improvement of pruritus (responder ratio)	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6 Reduction of lower leg volume (ml)	6	502	Mean Difference (IV, Random, 95% CI)	32.10 [13.49, 50.72]
7 Reduction of circumference at ankle (mm)	3	80	Mean Difference (IV, Random, 95% CI)	4.71 [1.13, 8.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Reduction of circumference at calf (mm)	3	80	Mean Difference (IV, Random, 95% CI)	3.51 [0.58, 6.45]

Analysis 1.1. Comparison 1 HCSE versus placebo, Outcome 1 Improvement of leg pain (responder ratio).

Study or subgroup	HCSE n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Neiss 1976	132/209	91/209		2.22[1.5,3.29]

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours HCSE

Analysis 1.2. Comparison 1 HCSE versus placebo, Outcome 2 Reduction of leg pain (100 mm VAS).

Study or subgroup	HCSE N	HCSE Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cloarec 1992	15	42.6 (9.7)	15	0.2 (11.3)		42.4[34.9,49.9]

Favours placebo -100 -50 0 50 100 Favours HCSE

Analysis 1.3. Comparison 1 HCSE versus placebo, Outcome 3 Reduction of oedema (100 mm VAS).

Study or subgroup	HCSE N	HCSE Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cloarec 1992	15	41.2 (9.3)	15	1.1 (14)		40.1[31.6,48.6]

Favours placebo -100 -50 0 50 100 Favours HCSE

Analysis 1.4. Comparison 1 HCSE versus placebo, Outcome 4 Improvement of oedema (responder ratio).

Study or subgroup	HCSE n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Neiss 1976	114/173	71/173		2.78[1.79,4.3]

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours HCSE

Analysis 1.5. Comparison 1 HCSE versus placebo, Outcome 5 improvement of pruritus (responder ratio).

Study or subgroup	HCSE n/N	Placebo n/N	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Neiss 1976	66/98	50/98		1.98[1.11,3.53]

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours HCSE

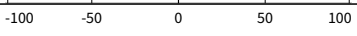
Analysis 1.6. Comparison 1 HCSE versus placebo, Outcome 6 Reduction of lower leg volume (ml).

Study or subgroup	HCSE N	HCSE Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Diehm 1992	20	84 (215)	19	4 (297)		1.3%	80[-83.44,243.44]
Diehm 1996a	95	43.8 (111.1)	46	-9.8 (101.7)		25.43%	53.6[16.68,90.52]
Diehm 2000	143	18 (75)	70	-2 (82)		66.64%	20[-2.81,42.81]
Rudofsky 1986	19	44.3 (155.3)	20	-33.9 (176)		3.2%	78.2[-25.85,182.25]
Steiner 1986	10	114 (265.5)	10	0.6 (260.6)		0.65%	113.4[-117.18,343.98]
Steiner 1990a	25	26.6 (171)	25	-4.5 (227.6)		2.78%	31.09[-80.5,142.68]
Total * **	**312**		**190**			**100%**	**32.1[13.49,50.72]**
Heterogeneity: Tau^2=0; Chi^2=3.95, df=5(P=0.56); I^2=0%							
Test for overall effect: Z=3.38(P=0)							

Favours placebo — Favours HCSE

Analysis 1.7. Comparison 1 HCSE versus placebo, Outcome 7 Reduction of circumference at ankle (mm).

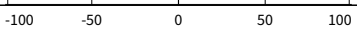
Study or subgroup	HCSE N	HCSE Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cloarec 1992	15	7.7 (18.4)	15	-4.3 (22.5)		5.92%	12[-2.69,26.69]
Pilz 1990	15	7 (5)	15	3 (6)		81.83%	4[0.05,7.95]
Steiner 1986	10	6 (12.3)	10	0.1 (11)		12.24%	5.9[-4.32,16.12]
Total * **	**40**		**40**			**100%**	**4.71[1.13,8.28]**
Heterogeneity: Tau^2=0; Chi^2=1.12, df=2(P=0.57); I^2=0%							
Test for overall effect: Z=2.58(P=0.01)							



Favours placebo — Favours HCSE

Analysis 1.8. Comparison 1 HCSE versus placebo, Outcome 8 Reduction of circumference at calf (mm).

Study or subgroup	HCSE N	HCSE Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cloarec 1992	15	6.1 (35.9)	15	-2.3 (27.4)		1.65%	8.4[-14.43,31.23]
Pilz 1990	15	5 (4)	15	1 (5)		81.92%	4[0.76,7.24]
Steiner 1986	10	1.3 (9.7)	10	0.7 (6.6)		16.43%	0.6[-6.64,7.84]
Total * **	**40**		**40**			**100%**	**3.51[0.58,6.45]**
Heterogeneity: Tau^2=0; Chi^2=0.89, df=2(P=0.64); I^2=0%							
Test for overall effect: Z=2.35(P=0.02)							



Favours placebo — Favours HCSE

Comparison 2. HCSE versus compression

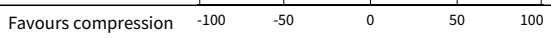
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of lower leg volume (ml)	2	479	Mean Difference (IV, Random, 95% CI)	-37.34 [-104.07, 29.39]
2 Improvement of symptom score (40 point scale)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 HCSE versus compression, Outcome 1 Reduction of lower leg volume (ml).

Study or subgroup	HCSE N	HCSE Mean(SD)	compression N	compression Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Diehm 1996a	95	43.8 (111.1)	99	46.7 (81.6)		49.43%	-2.9[-30.42,24.62]
Diehm 2000	143	18 (75)	142	89 (122)		50.57%	-71[-94.53,-47.47]
Total ***	**238**		**241**			**100%**	**-37.34[-104.07,29.39]**

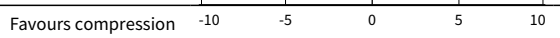
Heterogeneity: Tau²=2148.14; Chi²=13.59, df=1(P=0); I²=92.64%

Test for overall effect: Z=1.1(P=0.27)



Analysis 2.2. Comparison 2 HCSE versus compression, Outcome 2 Improvement of symptom score (40 point scale).

Study or subgroup	HCSE N	HCSE Mean(SD)	compression N	compression Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Diehm 2000	143	4.9 (6.8)	142	4.6 (5.8)		0.38[-1.09,1.85]



Comparison 3. HCSE versus ß-hydroxyethyl-rutosides

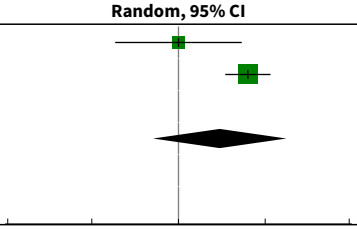
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of circumference at ankle (mm)	2	60	Mean Difference (IV, Random, 95% CI)	2.38 [-1.47, 6.23]
2 Reduction of circumference at calf (mm)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Reduction of leg pain (VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Leg volume (ml)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Reduction of oedema (VAS)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 HCSE versus ß-hydroxyethyl-rutosides, Outcome 1 Reduction of circumference at ankle (mm).

Study or subgroup	HCSE N	HCSE Mean(SD)	beta-HR N	beta-HR Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Erdlen 1989	15	4 (4)	15	4 (6)		40.55%	0[-3.65,3.65]
Kalbfleisch 1989	17	2 (1.9)	13	-2 (1.7)		59.45%	4[2.7,5.3]
Total ***	**32**		**28**			**100%**	**2.38[-1.47,6.23]**

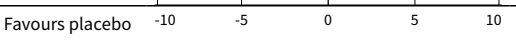
Heterogeneity: Tau²=6.05; Chi²=4.09, df=1(P=0.04); I²=75.56%

Test for overall effect: Z=1.21(P=0.23)



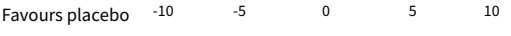
Analysis 3.2. Comparison 3 HCSE versus ß-hydroxyethyl-rutosides, Outcome 2 Reduction of circumference at calf (mm).

Study or subgroup	HCSE N	HCSE Mean(SD)	beta-HR N	beta-HR Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kalbfleisch 1989	17	1.8 (3.9)	13	-5 (3.2)		6.8[4.26,9.34]



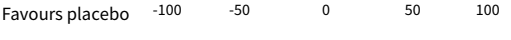
Analysis 3.3. Comparison 3 HCSE versus ß-hydroxyethyl-rutosides, Outcome 3 Reduction of leg pain (VAS).

Study or subgroup	HCSE N	HCSE Mean(SD)	beta-HR N	beta-HR Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kalbfleisch 1989	17	1.9 (3.6)	13	1.2 (3)		0.65[-1.74,3.04]



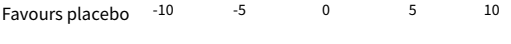
Analysis 3.4. Comparison 3 HCSE versus ß-hydroxyethyl-rutosides, Outcome 4 Leg volume (ml).

Study or subgroup	HCSE N	HCSE Mean(SD)	beta-HR N	beta-HR Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Rehn 1996	51	26 (99)	51	46.4 (132)		-20.4[-65.68,24.88]



Analysis 3.5. Comparison 3 HCSE versus ß-hydroxyethyl-rutosides, Outcome 5 Reduction of oedema (VAS).

Study or subgroup	HCSE N	HCSE Mean(SD)	beta-HR N	beta-HR Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kalbfleisch 1989	17	0.7 (3.8)	13	1.6 (3.5)		-0.93[-3.52,1.66]



APPENDICES

Appendix 1. Search strategy for CENTRAL 2012

#1	MeSH descriptor Venous Insufficiency explode all trees	337
#2	insuffic* or CVI or isch*	30384
#3	(#1 OR #2)	30409
#4	MeSH descriptor Escin explode all trees	53
#5	aesculus*	31
#6	escin* or aescin* or essaven*	113
#7	rosskastani*	16
#8	horse* near (chestnut or chest-nut)	54
#9	venosta*	25
#10	(#4 OR #5 OR #6 OR #7 OR #8 OR #9)	171
#11	(#3 AND #10)	37

Appendix 2. Search strategy for Amed and Phytobase

Search strategy
horse chestnut Aesculus hippocastanum escin venostasin Rosskastanie [Rosskastanie is the German common name for Aesculus hippocastanum L.]

Appendix 3. Search strategy for CENTRAL 2010

#1	MeSH descriptor Venous Insufficiency explode all trees	303
#2	insuffic* or CVI or isch*	26623
#3	(#1 OR #2)	26646
#4	MeSH descriptor Escin explode all trees	52

(Continued)

#5	aesculus*	30
#6	escin* or aescin* or essaven*	101
#7	rosskastani* or roskastani*	14
#8	horse* near chest*	49
#9	venosta*	23
#10	(#4 OR #5 OR #6 OR #7 OR #8 OR #9)	156
#11	(#3 AND #10)	37

Appendix 4. Search strategy for CENTRAL 2008

	Number of records retrieved
#1 MeSH descriptor Venous Insufficiency explode all trees	271
#2 (ven* or chron*) near insuffic*	1366
#3 (#1 OR #2)	1382
#4 MeSH descriptor Escin explode all trees	50
#5 aesculus* near hippocastan*	16
#6 escin* or aescin* or essaven*	97
#7 rosskastani*	14
#8 horse* near (chestnut or chest-nut) near seed*	29
#9 venosta*	23
#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)	136
#11 (#3 AND #10)	37

WHAT'S NEW

Date	Event	Description
23 October 2012	Review declared as stable	No new included studies have been identified since 2005. This Cochrane review has been marked stable and will only be updated when new studies are identified.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 1, 2002

Date	Event	Description
19 June 2012	New search has been performed	Searches re-run, no new trials found. The review was assessed as up to date.
19 June 2012	New citation required but conclusions have not changed	Searches re-run, no new trials found. Minor copy edits made, conclusions not changed.
27 July 2010	New search has been performed	Searches re-run and four additional studies were excluded from the review. Risk of bias tables added to the Included studies and minor changes made to the text of the review.
22 September 2008	New search has been performed	Searches re-run, no new trials found. Minor changes to the text of the review.
22 September 2008	Amended	Converted to new review format.
15 February 2007	Amended	Search dates changed, no new trials found. Plain language summary added and minor copy edits.
15 November 2005	New citation required but conclusions have not changed	Substantive amendment. One additional trial included but no change to conclusions.
25 February 2004	New citation required but conclusions have not changed	Substantive update. One additional trial included but no change to conclusions.

CONTRIBUTIONS OF AUTHORS

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DECLARATIONS OF INTEREST

None known

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INDEX TERMS

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*Aesculus [adverse effects]; *Seeds; Administration, Oral; Chronic Disease; Leg [*blood supply]; Pain [drug therapy]; Phytotherapy [adverse effects] [*methods]; Plant Extracts [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome; Venous Insufficiency [*drug therapy]

MeSH check words

Humans