Horse-Chestnut Seed Extract for Chronic Venous Insufficiency

A Criteria-Based Systematic Review

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Objective: To assess the evidence for or against horse-chestnut seed extract (HCSE) as a symptomatic treatment of chronic venous insufficiency (CVI).

Data Sources: Computerized literature searches were performed in MEDLINE, EMBASE, BIOSIS, CISCOM, and the Cochrane Library (all from their respective institution to December 1996). The search terms were “horse chestnut,” “Aesculus hippocastanum,” “escin,” and “Rosskastanie” (German for “horse chestnut”). There were no restrictions on the language of publication.

Study Selection: Double-blind, randomized controlled trials of oral HCSE for patients with CVI were included. Identifiers were removed from all publications before assessment.

Data Extraction: Data were extracted in a standardized, predefined manner. Trial outcomes and the methodological quality of each trial were independently assessed by the 2 reviewers.

Data Synthesis: The superiority of HCSE is suggested by all placebo-controlled studies. The use of HCSE is associated with a decrease of the lower-leg volume and a reduction in leg circumference at the calf and ankle. Symptoms such as leg pain, pruritus, and a feeling of fatigue and tenseness are reduced. Five comparative trials against the reference medication indicate that HCSE and O-(β-hydroxyethyl)-rutosides are equally effective. One trial suggests a therapeutic equivalence of HCSE and compression therapy. Adverse effects are usually mild and infrequent.

Conclusions: These data imply that HCSE is superior to placebo and as effective as reference medications in alleviating the objective signs and subjective symptoms of CVI. Thus, HCSE represents a treatment option for CVI that is worth considering.

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With a prevalence of 10% to 15% in men and 20% to 25% in women, chronic venous insufficiency (CVI) is among the most common conditions afflicting humans. It is more than a mere “cosmetic problem” because patients often require hospital admission and surgical treatment. At least two thirds of leg ulcers have evidence of venous disease in the affected limb. The burden of suffering is high, and the economic costs for society are considerable. Although the therapy of choice is mechanical compression, compliance is often poor, which renders oral drug treatment an attractive option.

Horse chestnut (Aesculus hippocastanum) is an herbal remedy traditionally used for CVI. Horse-chestnut seed extract (HCSE), the active component of which is escin, a triterpenic saponin, has shown enzyme-inhibiting activity. The accumulation of leukocytes in CVI-affected limbs with their subsequent activation is considered an important pathophysiological mechanism of CVI. Horse-chestnut seed extract may work by preventing leukocyte activation. Regardless of the postulated mechanism of action, the most important question concerns HCSE’s clinical effectiveness. Our aim in this systematic review is to summarize the evidence from randomized controlled trials (RCTs) for or against the effectiveness of HCSE in the symptomatic treatment of CVI.

Sixteen RCTs were retrieved. Relevant unpublished trials were not found. Three studies had to be excluded from this review, because they were duplicate publications and because it was not conducted with an HCSE monopreparation.
TRIALS AND METHODS

Computerized literature searches were performed to identify all RCTs of HCSE for CVI. Databases included MEDLINE, EMBASE, BIOSIS, CISCOM, and the Cochrane Library (all from their respective institution to December 1996). The search terms used were “horse chestnut,” “Aesculus hippocastanum,” “escin,” and “Rosskastanie” (German for “horse chestnut”). All manufacturers of HCSE preparations were asked to contribute published and unpublished material, and our own extensive files were scanned. The bibliographies of the studies thus retrieved were searched for further trials. There were no restrictions on the language of publication.

Identifiers of all publications were concealed by eliminating (by a person not involved in the review) the names of the author(s), journal, and institution before assessment. Trial outcomes and the methodological quality of each trial were independently assessed by both of us using a standard scoring system to measure the likelihood of bias (Table 1). Disagreements in the evaluation of individual trials were resolved by discussion. Randomized controlled trials were included if performed on patients with CVI treated with HCSE monopreparations and if conducted double blind against placebo or the reference medication. Articles scoring below 3 (maximum, 5) points on the quality scale were excluded. A meta-analysis of trial results for leg-volume assessment in placebo-controlled RCTs had initially been planned. Because of variations in devices used for assessment and insufficient reporting of data, this plan had to be abandoned.

Thirteen studies (16-28) fulfilled the inclusion-exclusion criteria. Eight of these (16-23) were placebo controlled, and 5 (24-28) were controlled against reference medications. All trials scored at least 3 points on a standard scoring system to measure the likelihood of bias. Two trials (16,21) scored 5 points on this scale, suggesting the superiority of the use of HCSE over placebo for the symptomatic treatment of CVI. Table 2 summarizes key data of all included trials ranked in a hierarchical order according to their methodological quality score.

The placebo-controlled RCTs suggest a decrease in lower-leg volume and a reduction in leg circumference at the calf and ankle with the use of HCSE. Edema provoked before and after the treatment period revealed protective effects against edema. A decrease of the capillary filtration rate by 22% in HCSE-treated patients was suggested. The prevalence of symptoms such as leg pain, pruritus, and the feeling of fatigue and tenseness was reduced. All 5 RCTs against reference medications demonstrated evidence for the effectiveness of HCSE for the treatment of CVI. Although in 1 study, HCSE was stated to be superior to O-(β-hydroxyethyl)-rutosides in protecting against edema, most trials suggest that both drugs are of equal value. One trial (20) suggests a therapeutic equivalence of HCSE and compression therapy. This trial was not properly blinded, however, so its results are subject to bias.

Significant beneficial effects for patients with CVI are reported in trials that administered HCSE standardized to 100 to 150 mg of escin per day. Two studies (16,23) assessing the use of 100 mg of escin per day found a significant (P < .001 and P = .009, respectively) reduction of mean leg volumes after 2 weeks of treatment compared with placebo. The persistence of treatment effects is suggested by 1 study (25). At the end of a 6-week follow-up, the mean leg volume was not significantly different from posttreatment values. Most studies used the classification system by Widmer and Stahelin for categorizing patients and defining inclusion criteria (stage I: ankle edema without trophic changes; stage II: edema, hyperpigmented or depigmented areas, indurations; stage III: open or healed leg ulcer). Because no universally accepted classification of CVI exists to date, this seems the best available. Eleven trials (16-20,23-28) used criteria of this classification system for including patients with CVI. Of the 1083 studied patients, 388 (35.8%) were categorized into CVI stages I to II. Three studies (17,20,26) included patients with stages I to III. Two trials (21,22) comprising 29% of the studied patients, did not refer to this classification. The placebo response in trials assessing subjective variables as the main end point ranged from 20% to 27%. Changes of objective variables during placebo use are summarized in Table 2.

Eight studies (16,18,20-23,25,26) reported on adverse drug reactions (ADRs). Gastrointestinal tract symptoms, dizziness, nausea, headache, and pruritus were reported. The reported frequency of ADRs ranged from 0.9% to 3.0%. In 3 studies, (18,21,23) the frequency of ADRs was not significantly different from that of placebo.

### Table 1. Scoring System to Measure the Likelihood of Bias*

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study described as randomized (this includes the use of words such as “random,” “randomly,” and “randomization”)?</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>2. Study described as double blind?</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>3. Description of withdrawals and dropouts?</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>4. Method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc)?</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5. Method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>6. Method to generate the sequence of randomization described and inappropriate (patients were allocated alternately or according to their date of birth, hospital number, etc).</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>7. Method of double blinding described and inappropriate (eg, comparison of tablet vs injection with no double dummy).</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

*Adapted from Jadad et al. For questions 1 through 5, each yes answer equals 1 point, and each no answer equals 0 points. Deduct 1 point if question 6 or 7 apply.

**COMMENT**

This criteria-based, systematic review suggests that HCSE is an effective therapy for CVI. Experts from Europe and the United States, however, remain unconvinced of its effectiveness for this condition. Herbal medicine is clearly more accepted in German-speaking countries than...
Thus, it is not surprising that most of the studies are published by German authors. This may be 1 reason why this treatment option has gone unappreciated by English-speaking clinicians.

Even though our search strategy was comprehensive, that some trials have been missed cannot be entirely ruled out. Trials with negative results have a tendency to remain unpublished. In particular, in journals of complementary or alternative medicine, studies with positive findings may be overrepresented. The results of these trials might conceivably be biased and, thus, present a false-positive picture. All trials scored at least 3 of 5 points on a scale assessing the likelihood of bias (Table 1). Two studies reporting that HCSE was superior to placebo scored the maximum of 5 points. Despite this, none of the studies were completely flawless. Thus, the uncertain quality of the original data might be another source of bias. Future trials of CVI should be executed and reported in a uniform manner to enable subsequent statistical pooling in meta-analyses. Attention must be paid to the control of patient compliance, and the assessment of venous function would require standardization. Randomization and double-blinding procedures should be detailed in the published reports. Finally, carryover effects in crossover studies need to be taken into account.

If, despite these caveats, HCSE is accepted as effective therapy for CVI, its mechanism of action may be of interest. The active component of HCSE is the saponin es-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Quality Score (Maximum 5)</th>
<th>Study Design</th>
<th>No. of Patients Entered/No. of Dropouts</th>
<th>Medication (Dosage)</th>
<th>Treatment Period</th>
<th>Compliance Monitored/ADRs Mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudofsky et al, 1986</td>
<td>5</td>
<td>2 Parallel groups</td>
<td>40/1</td>
<td>HCSE (1 capsule twice a day)†</td>
<td>4 wk</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Bisler et al, 1986</td>
<td>5</td>
<td>Crossover</td>
<td>24/2</td>
<td>HCSE (2 capsules once a day)†</td>
<td>NA</td>
<td>NA/No</td>
</tr>
<tr>
<td>Pilz, 1990</td>
<td>4</td>
<td>2 Parallel groups</td>
<td>30/2</td>
<td>HCSE (1 capsule twice a day)†</td>
<td>20 d</td>
<td>No/Yes</td>
</tr>
<tr>
<td>Diehm et al, 1992</td>
<td>4</td>
<td>2 Parallel groups</td>
<td>40/1</td>
<td>HCSE (1 capsule twice a day)‡</td>
<td>6 wk</td>
<td>No/No</td>
</tr>
<tr>
<td>Friederich et al, 1978</td>
<td>4</td>
<td>Crossover</td>
<td>118/23</td>
<td>HCSE (1 capsule twice a day)</td>
<td>20 d</td>
<td>No/Yes</td>
</tr>
<tr>
<td>Lohr et al, 1986</td>
<td>3</td>
<td>2 Parallel groups</td>
<td>80/6</td>
<td>HCSE (1 capsule twice a day)</td>
<td>8 wk</td>
<td>No/Yes</td>
</tr>
<tr>
<td>Neiss and Böhm, 1976</td>
<td>3</td>
<td>Crossover</td>
<td>233/7</td>
<td>HCSE (1 capsule twice a day)†</td>
<td>20 d</td>
<td>No/Yes</td>
</tr>
<tr>
<td>Steiner, 1990</td>
<td>3</td>
<td>Crossover</td>
<td>20/NR</td>
<td>HCSE (1 capsule twice a day)†</td>
<td>2 wk</td>
<td>No/Yes</td>
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<tr>
<td>Kalbfleisch and Pfalzgraf, 1989</td>
<td>4</td>
<td>2 Parallel groups</td>
<td>33/3</td>
<td>HCSE (1 capsule once a day), HR (500 mg/d)†</td>
<td>8 wk</td>
<td>No/No</td>
</tr>
<tr>
<td>Rehn et al, 1996</td>
<td>4</td>
<td>3-Armed parallel groups</td>
<td>155/18</td>
<td>HCSE (1 capsule twice a day), HR (1000 mg/d [loading dose for 4 wk, then 500 mg/d [for 8 wk])†</td>
<td>12 wk</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Diehm et al, 1996</td>
<td>3</td>
<td>3-Armed parallel groups</td>
<td>240/NR</td>
<td>HCSE (1 capsule twice a day); (compression therapy/placebo)</td>
<td>12 wk</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Erdlen, 1989</td>
<td>3</td>
<td>2 Parallel groups</td>
<td>30/NR</td>
<td>HCSE (1 capsule twice a day)§</td>
<td>4 wk</td>
<td>No/No</td>
</tr>
<tr>
<td>Erler, 1991</td>
<td>3</td>
<td>2 Parallel groups</td>
<td>40/NR</td>
<td>HCSE (1 capsule twice a day), HR (2000 mg/d)‡</td>
<td>8 wk</td>
<td>No/No</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1083/63</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*ADRs indicate adverse drug reactions; NA, not applicable; CFC, capillary filtration coefficient; NR, not reported; and HR, O-β-hydroxyethyl)-rutosides. Verum is equivalent to HCSE.
†Standardized to 50 mg of escin.
‡Standardized to 75 mg of escin.
§Reference medication was not defined.
||Not all trials reported the number of withdrawals or dropouts.
ported by a study of animals36; using electromicroscopy, it
venting vascular leakage. This hypothesis has been sup-
thesis of proteoglycans toward a net synthesis, thus pre-
may shift the equilibrium between the degradation and syn-
tivity of proteoglycan hydrolases in patients with CVI that
enzymes.11 An earlier study35 found increased serum ac-
gest a possible subsequent activation with the release of such
creased levels of leukocytes in CVI-affected limbs and sug-
erwelling.

The conservative treatment of CVI comprises a
variety of other modalities. Compression therapy
improves venous return and is widely accepted as the
treatment of choice.37 In combination with heparin, it
prevents venous stasis and reduces the risk of deep-
vein thrombosis. The use of O-(β-hydroxyethyl)-
rutosides has beneficial short-term effects by reducing
edema and relieving symptoms of CVI. Its efficacy
during long-term use has yet to be established, how-
ever.38 The extract of Ruscus aculeatus decreases the
capillary filtration rate in healthy volunteers and
patients with CVI.39 One recent review40 concludes
that combined treatment with edema protective agents
and compression therapy has a better clinical benefit
than either treatment alone.

Pruritus, nausea, gastrointestinal tract symptoms,
headache, and dizziness were reported as ADRs to HCSE.
In 3 studies,18,21,23 the frequency of ADRs with HCSE use
was not significantly different from that with placebo. In
a recent observational study41 involving more than 5000
patients with CVI, ADRs occurred in 0.6% of patients
during treatment with HCSE. Gastrointestinal tract symp-
toms and calf spasm were reported most frequently. Ad-
verse drug reactions are also reported from other
symptomatic treatment options for CVI. Those of Rusc-
us extract include gastrointestinal tract symptoms and
nausea, and ingesting O-(β-hydroxyethyl)-rutosides can
cause allergic skin reactions.32 About a third of Scottish
surgeons reported43 at least 1 case of skin necrosis or ul-
cers induced by compression therapy. These cumulative
data imply that HCSE use is relatively safe.

The evidence presented here implies that HCSE is safe
and effective as a symptomatic, short-term treatment
of CVI. Publication bias and methodological short-
comings are important caveats. More rigorous RCTs
are required to verify the usefulness of the treatment,
especially for long-term use and as an adjunct to com-
pression therapy.

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