Treatment of Patients With Venous Insufficiency With Fresh Plant Horse Chestnut Seed Extract: A Review of 5 Clinical Studies

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ABSTRACT

Extracts from the seed of the horse chestnut (*Aesculus hippocastanum* L.) have traditionally been used to treat patients with chronic venous insufficiency and to alleviate its associated symptoms, including lower leg swelling. The efficacy of preparations that contain horse chestnut seed extract (HCSE) is believed to be due largely to an inhibitory effect on the catalytic breakdown of capillary wall proteoglycans. Aesculaforce® is a fresh plant HCSE that is available as an oral tincture, as tablets (20 mg or 50 mg), and as topical gel. Four clinical trials in patients with chronic venous insufficiency and 1 study in patients with varicose veins demonstrated the effectiveness of these preparations through the objective measure of reduction in lower leg edema and the subjective alleviation of leg pain, heaviness, and itching. Safe, well tolerated, and acceptable to patients, the fresh plant HCSE preparation Aesculaforce offers a real alternative in the treatment of patients with mild to moderate venous insufficiency.

Keywords: horse chestnut seed extract; clinical trial; chronic venous insufficiency; edema; varicose veins

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INTRODUCTION

The horse chestnut (*Aesculus hippocastanum* L.) is native to southeast Europe; its large, globular, brown seeds are a staple in folk medicine and traditionally served as a treatment for patients with dysentery, bronchitis, hemorrhoids, and venous problems. Clinical use of horse chestnut seed extract (HCSE) for chronic venous disease began several decades ago, and published data support its use in chronic venous insufficiency to alleviate pain, heaviness, nocturnal cramps, itching, and edema in the legs.[1]

In most industrialized countries, chronic venous insufficiency affects from 6% to 10% of adults, and prevalence rises significantly with age.[2] The Edinburgh Vein Study, which screened 1566 participants, identified the disorder in 21.2% of the men and in 12.0% of the women older than 50 years.[3] The disease is characterized by venous stasis due to valvular incompetence, principally caused by inflammation or venous occlusion. Early signs (stage I) include edema of the calf and ankles, which results from increased capillary permeability and filtration of fluid, electrolytes, and low-molecular-weight proteins into the interstitium. The more superficial effects of this process are seen as varicose veins. Skin alterations, including hyperpigmentation, eczema, and induration, are seen in stage II disease.

The active constituents of HCSE, collectively known as aescin (3%–10%), comprise a mixture of alkylated triterpene glycosides (saponins). Flavonoids, sterols, essential oils, and starch are also present. The efficacy of HCSE-containing preparations is believed to be due largely to an inhibitory effect on the catalytic breakdown of capillary wall proteoglycans,[4,5] which possibly occurs through a protective action on the fragile lysosomal membrane that is the site of enzyme release.[6] Additionally, HCSE has anti-inflammatory[7] and potent vasoconstrictive[8] properties; it exerts a positive influence on venous tone and increases the flow velocity of venous blood.[9]

In chronic venous insufficiency, *Aesculus* preparations are reportedly and in accordance with the Cochrane Collaboration assessment superior to placebo in alleviating pain, tiredness, tension, and pruritus and in significantly reducing edema of the upper leg and ankle.[10] Clinical trials have shown HCSE to be as effective as 0-β-hydroxyethyl-rutoside[11-13] and compression therapy.[14]

Preclinical safety studies revealed no chronic oral toxicity or teratogenic or relevant mutagenic activity. In clinical studies of chronic venous insufficiency, HCSE demonstrated excellent tolerability, with an adverse reaction rate from 0.9% to 3.0%. Gastrointestinal disturbances, dizziness, headache, and itching were most frequently reported.[15]

This report reviews 5 clinical studies in patients with chronic venous insufficiency and varicose veins that investigated the safety and efficacy of 4 HCSE formulations that contain the fresh plant extract Aesculaforce® (Bioforce AG, Roggwil, Switzerland). An alcohol extract made from fresh plant horse chestnut seed, Aesculaforce is formulated as a tincture, as tablets, and as gel. It has been marketed since 1978 and is available in 17 countries.

MATERIALS AND METHODS

The following formulations of Aesculaforce were investigated in these clinical studies:

- Alcohol tincture of fresh horse chestnut seeds—drug extract ratio, 1:2.6; dosage regimen equivalent to 1.5 g of fresh plant material (or 0.8 g of dried material); contains 39 mg of aescin.

- Tablets, 20 mg aescin, hereafter referred to as 20-mg tablets; gastroresistant and film coated; contain 63 to 90 mg of native extract from fresh horse chestnut seed (drug extract ratio, 5.0–6.1:1) and 20 mg of aescin. Dosage is 1 to 2 oral tablets 3 times daily.
- Tablets, 50 mg aescin, hereafter referred to as 50-mg tablets; gastroresistant and film coated; contain 157.5 to 225 mg of native extract from fresh horse chestnut seed (drug extract ratio, 5.0–6.1:1) and 50 mg of aescin. Dosage is 1 oral tablet twice daily.
- Gel, 2% aescin; 1 g of gel contains 54 to 117 mg of native extract from fresh horse chestnut seed (drug extract ratio, 5.0–6.1:1). The product is applied topically twice daily.

Studies of the tablets and gel were conducted in compliance with the guidelines of Good Clinical Practice, and protocols were approved by the relevant local independent ethics committee.[1] Patients gave written consent to participate before they underwent any study-specific procedures. Table 1 provides details of the study designs and assessment variables.

RESULTS

Aesculaforce Tincture

Efficacy data were available for 38 patients at the end of an average of 4 weeks of treatment in this study of chronic venous insufficiency. Table 2 lists global efficacy ratings and effects on symptoms. In terms of global efficacy, a clinically relevant therapeutic result occurred in 77% of patients; more than 60% of patients rated efficacy as "good" to "very good" for the symptoms of leg swelling, pruritus, sensations of heaviness and tension in the legs, and calf cramps.

Three adverse events were reported; 2 (vomiting/malaise, "foul taste") resulted in withdrawal from the study. One patient complained of heartburn/bitterness but completed treatment. The tincture was well tolerated.

Aesculaforce Tablets (20 mg)

A total of 52 patients completed this randomized, placebo-controlled, double-blind study.[16] Two patients were withdrawn for noncompliance, and 3 each in the test substance and placebo groups discontinued because of adverse reactions. These included 3 reports of gastrointestinal problems (2 placebo, 1 test substance) that were possibly or probably related to the study medication. Compliance was not evaluated because many patients did not return the remaining tablets.

Table 3 shows efficacy results. Statistical analysis used a 2-factorial variance design (Friedman's test) at a significance level of .05. Symptoms improved in both groups. The test substance group achieved a clinically relevant, statistically significant reduction in ankle circumference compared with the placebo group, which showed no change ($P<.05$). Calf-refilling time also rose significantly with verum tablets. The global tolerability scores assessed by patients and physicians showed no between-group differences versus placebo.

Table 1. Studies of Aesculaforce in Chronic Venous Insufficiency and Varicose Veins: Designs and Assessment Variables

Formulation/Dosage	Design	Patients	Treatment Duration, Wk	Assessment Variables
Tincture, 25 drops, TID orally	Prospective, open, uncontrolled, multicenter	CVI stage I/II n=40: 32 women, 8 men (mean age, 56 y)	3–8 (mean, 4)	**Efficacy** Global evaluation (patient and physician), effect on symptoms **Safety** Adverse events
Tablets, 20 mg, 2 tablets TID orally	Randomized, placebo controlled, multicenter, double blind	CVI stage I/II n=60: 56 women, 4 men, 30 Aesculaforce, 30 placebo (mean age, 55 y)	6	**Primary Efficacy** Circumference of more severely affected leg measured just above ankle **Secondary Efficacy** Summed score of subjective symptoms (heaviness/tension, pain, itching, paresthesia), digital venous or PPG measurement of calf-refilling rate **Tolerability** Adverse events, global score (patient and physician)
Tablets, 50 mg, 1 tablet BID orally	Open, single center	CVI stage I/II n=87 (mean age, 51 y)	8	**Primary** Safety as assessed by all adverse events **Secondary** Tolerability (patient and physician) **Efficacy** Changes in symptom scores (patient and physician), circumference of ankle and lower leg, venous circulation of affected lower limb by PPG, overall assessment (patient and physician), overall acceptance of treatment (patient)
Gel, applied morning and evening to lower legs, ankles, and inner thigh	Open, uncontrolled, multicenter	CVI-induced edema n=71: 61 women, 10 men (age, 20–91 y)	6	**Efficacy** Ankle circumference, total symptom score, overall efficacy (patient and physician) **Safety** Adverse events, tolerability (patient and physician), acceptance of treatment (patient)

cont'd

Table 1. Studies of Aesculaforce in Chronic Venous Insufficiency and Varicose Veins: Designs and Assessment Variables, cont'd

Formulation/Dosage	Design	Patients	Treatment Duration, Wk	Assessment Variables
Gel, applied BID with or without 20-mg tablets, 1 tablet TID plus massage therapy	Open, uncontrolled	CVI stage I/II varicose veins, pregnant (groups 1 and 2) and nonpregnant (groups 3 and 4) patients (n) (mean age, 39 y): group 1—massage and gel (4); group 2—massage only (7); group 3—massage and gel (22); group 4—massage, gel, and tablets (20)	10–12 (minimum 8 for inclusion in analysis)	**Subjective** Symptom scores by VAS (patient and therapist), efficacy and tolerability of gel and tablets, comments on gel smell, spreadability, stickiness, and color **Objective** Reduction of ankle edema

TID=three times daily; CVI=chronic venous insufficiency; PPG=photoplethysmography; BID=twice daily; VAS=visual analogue scale.

Table 2. Aesculaforce Fresh Plant Tincture: Symptom Scores

	Global Assessment, n (%)			
	Effective	Moderately Effective	Slightly Effective	Ineffective
Physician (n=38)	22 (57.9)	9 (23.7)	5 (13.2)	2 (5.3)
Patient (n=38)	24 (63.2)	9 (23.7)	3 (7.9)	2 (5.3)
	Efficacy Assessment, n (%)			
	Very Good	Good	Moderate	No Effect
Pain (n=21)	5 (23.8)	3 (14.3)	7 (33.3)	6 (28.6)
Swelling (n=28)	6 (21.4)	11 (39.3)	8 (28.6)	3 (10.7)
Pruritus (n=6)	1 (16.7)	3 (50.0)	2 (33.3)	0
Heaviness (n=31)	6 (19.4)	16 (51.5)	3 (9.7)	6 (19.4)
Tension (n=28)	7 (25.0)	16 (57.1)	5 (17.9)	0
Calf cramps (n=13)	6 (46.2)	5 (38.5)	2 (15.4)	0

Table 3. Aesculaforce Fresh Plant 20-mg Tablets: Efficacy Results

Variable	Result	Statistical Analysis*
Ankle circumference after 6 wk	Decrease of 0.5 cm at 2 wk (study group) No further change at 6 wk No change at 6 wk in placebo group	F group × time=3.144; $P<.05$
Summed symptom score†	Significant ↓ in both groups No significant difference between groups	F time=142.12; $P<.0001$ F group × time=0.115; $P=.89$
Calf refilling‡	Increase from 23 to 30 sec in study group at 6 wk No change in placebo group	F group × time=3.661; $P=.038$

*Friedman's test. 0.5-cm decrease at 2 wk.
†Each symptom scored from 0 (not present) to 5 (very pronounced).
‡Time to achieve maximum volume increase.

Aesculaforce Tablets (50 mg)

In all, 78 patients constituted the intent-to-treat (ITT) population.[17] Twelve patients discontinued this open study early, 5 as a result of adverse events. Compliance with medication, as assessed by counting of returned tablets, was high; more than 60 patients had a compliance rate of at least 75%.

Safety was the primary assessment variable in this study. Fifty-seven of the 87 patients recruited reported 91 adverse events (all nonserious), and only 4 were judged to be related to the study medication. One case was mild (transient "nausea"), and 3 were severe ("sore stomach" that resolved on reduction of daily dose, "bad wind," and "stomach pain").

At the end of treatment, 95% of ITT patients rated the tolerability of the study medication as "good" or "fairly good." Only 2 patients described tolerability as "poor." Assessment by physicians was similar (92% "good"/"fairly good").

Efficacy results are shown in Table 4. Median values had a nonnormal distribution and were analyzed by means of Wilcoxon's signed rank test. Lower leg and ankle circumferences decreased, albeit nonsignificantly Mean symptom scores improved significantly after 8 weeks of treatment.

Table 4. Aesculaforce Fresh Plant 50-mg Tablets: Efficacy Results

Variable	Results		*P* Value*
Symptom scores†	**Visit 1**	**Visit 3**	
Heaviness/tension	1.7 (0.79)	0.8 (0.88)	<.001
Pain	1.3 (0.92)	0.4 (0.67)	<.001
Burning	0.7 (0.88)	0.2 (0.56)	<.01
Itching/paresthesia	0.9 (0.94)	0.3 (0.67)	<.001
Ankle and lower leg circumferences	Both decreased at study end		NS
PPG	No significant changes; problems with validation of measurement method		
Overall efficacy	"Good" or "very good": 51% of patients No effect: 13% (n=10)		
Overall acceptance of treatment	81% would use vein tablets again No change in placebo group		

NS=nonsignificant.

*Wilcoxon's signed rank test.
†Mean (SD).

Aesculaforce Gel

Seventy-one patients participated in this open study of chronic venous insufficiency; 64 completed the 6-week treatment period and were included in the per-protocol evaluation.[18] Efficacy was determined through comparisons of ankle circumference and symptom scores by means of Wilcoxon's signed rank test, with a 1-tailed significance level of .05.

More than 85% of patients and physicians rated overall efficacy as "good" or "moderate." Ankle circumference and mean individual and total symptom scores all decreased significantly (Table 5).

Table 5. Aesculaforce Fresh Plant Gel: Efficacy Results

Variable	Results		*P* Value*
Ankle circumference	Mean 0.7-cm decrease over 6 wk		<.001
Symptom scores†	Baseline	Week 6	<.001
Edema	2.0 (0.9)	1.0 (0.8)	<.001
Heaviness/tension	2.5 (1.0)	1.0 (0.8)	<.001
Pain	2.2 (1.2)	0.8 (0.8)	<.001
Burning	1.0 (1.3)	0.2 (0.5)	<.001
Itching	0.7 (1.2)	0.2 (0.5)	<.001
Paresthesia	0.5 (1.1)	0.2 (0.5)	.0015
Total score	Mean decrease from 8.9 (baseline) to 4.8 (wk 3) and 3.4 (wk 6)		<.001 (baseline to wk 3) <.001 (wk 3 to wk 6)
Overall efficacy, %	**Patient**	**Physician**	
Good	57.8	59.4	
Moderate	29.7	26.6	
Weak	10.9	10.9	
Inactive	1.6	3.1	

*Wilcoxon's signed rank test.
†Mean (SD).

Eighteen adverse events—all considered to be unrelated to the gel—were reported by 13 of the 71 patients (18%) entered. Tolerability was rated "good" by 92% of patients and 98% of physicians. The compliance rate was 98.5%, and all patients were at least 70% compliant. Three fourths of patients stated that they would use the gel again.

Aesculaforce Gel and Tablets (20 mg) Combined

Thirty-nine patients (74%) with varicose veins completed more than 8 weeks of the study and were included in the analyses; 1 in the massage-only group completed the study. Compliance with tablets (2.4 tablets/d) was 80%; an average of 4.4 mL of gel was applied daily.

Nonparametric statistical analysis used Wilcoxon's matched-pairs test. Table 6 shows results for symptom scores and ankle edema. Heaviness and pain in the legs as well as blue discoloration were all significantly improved at the end of follow-up. Ankle edema also decreased.

Scores for efficacy/satisfaction and tolerability of the combined treatment, provided by both therapists and patients, were between 5 and 8 on a 10-point scale, indicating a moderate rating.

Table 6. Aesculaforce Fresh Plant Gel and 20-mg Tablets: Results

Therapist Assessment (n=39)	Results		*P* Value*
Heaviness/tension†	1.7 (0.79)	0.8 (0.88)	<.001
Symptom scores†	**Start**	**End**	
Heavy legs	5.09 (2.95)	2.79 (2.59)	.0003
Painful legs	4.28 (2.95)	1.25 (1.61)	<.00000
Itching	1.14 (2.29)	0.67 (2.12)	.081
Paresthesia	0.52 (1.62)	0 (0)	.229
Blue discoloration ("spiders")	6.36 (2.16)	3.77 (2.19)	<.00000
Ankle edema, cm†			
Left	23.68 (2.36)	23.04 (2.90)	.0468
Right	23.73 (2.38)	23.08 (2.68)	.0837
Patient Assessment (n=39)			
Symptom scores†			
Heavy legs	5.21 (2.70)	2.89 (2.87)	.0037
Painful legs	4.07 (2.70)	1.92 (2.21)	.0365
Itching	0.73 (1.71)	0.86 (2.08)	.0507
Paresthesia	0.53 (1.48)	0.19 (0.47)	.280
Blue discoloration ("spiders")	6.45 (2.39)	3.71 (2.24)	<.00000

*Wilcoxon's signed rank test.
†Mean (SD).

DISCUSSION

Reduction in Lower Leg Swelling

Measurement of ankle and lower leg circumferences at baseline and after treatment provides objective evidence of reduction in swelling and therefore therapeutic effectiveness. Three of the 4 studies of chronic venous insufficiency with Aesculaforce used this assessment, and all showed a decrease in circumference after treatment with the investigated application forms. In the randomized, placebo-controlled study with the fresh plant 20-mg tablet, the reduction was statistically significant and occurred within the first 2 weeks.[16] No further change was seen at 6 weeks, presumably because the edema had been almost completely eliminated. This result is similar to those achieved with other HCSE products.[19-21] Besides the reduction in ankle circumference seen with the fresh plant 50-mg tablet, a clinically relevant reduction in ankle circumference occurred with the fresh plant gel over a 6-week study of treatment in chronic venous insufficiency; results from other placebo-controlled trials confirm that this outcome cannot be ascribed to a placebo effect. Ankle edema associated with varicose veins decreased as well with the gel or gel plus 20-mg tablets in combination with massage, but the separate effects of the different treatment components cannot be determined.

Although readings made with a tape measure could be considered inaccurate compared with those obtained with a water plethysmometer, this approach is widely accepted and was long familiar to researchers at the investigating centers.

Twelve weeks of HCSE (50 mg twice daily) demonstrated equivalence to compression with standard elastic stockings in reducing edema.[14] Further reductions with HCSE beyond 12 weeks may be possible in that a steady state had not been reached.[14]

Compliance with compression regimens as reported in the literature is only 47%, compared with 90% in the HCSE study, suggesting less effectiveness of compression in actual clinical practice. HCSE is therefore a favorable alternative to compression for the treatment of patients with lower leg edema due to chronic venous insufficiency.

Symptom Scores

All studies reported an improvement in the common symptoms of early chronic venous insufficiency with the fresh plant HCSE–based treatment. In the randomized trial, both the fresh plant 20-mg tablets and placebo alleviated symptoms. This result, observed in most published studies of HCSE in chronic venous insufficiency, is due to the pronounced psychological effects of medical care on these patients, particularly in the early stage (stage I) of disease. Among more severely affected patients (stage II), a greater reduction in symptom score occurred at week 6 in the Aesculaforce group than in the placebo group; this outcome failed to reach statistical significance (P=.0511).

In the open study of fresh plant 50-mg tablets, symptom scores indicated generally mild to moderate disease at baseline and virtual disappearance of symptoms by the end of treatment. In the open study with the fresh plant gel, the total symptom score fell significantly during the first 3 weeks of use, with a further significant decrease observed between weeks 3 and 6. Although it is difficult to interpret such results from open, uncontrolled studies, at the end of both trials, all symptoms were significantly less bothersome than at baseline. Moreover, these outcomes are congruent with the findings of 2 meta-analyses of *Aesculus* preparations in the treatment of patients with chronic venous insufficiency, in whom pain, leg fatigue, and itching all improved, albeit not always to a significant degree.[10,22]

Reductions in overall and individual symptom scores were also recorded in the fresh plant tincture study. A clinically relevant result in the global assessment of efficacy—a rating of "effective" or "moderately effective"—was achieved by 31 patients in the physician's assessment and 33 patients in the patient's assessment. Efficacy was rated "good" to "very good" by 60% to 84% of patients for all individual symptoms except leg pain (38%).

Symptom scores decreased among patients given the fresh plant gel or gel–tablets combination along with massage for varicose veins. Reductions were statistically significant for heaviness, pain, and blue discoloration. Application of the gel is likely responsible for the decrease in discoloration, which, in the therapists' experience, is not affected by massage alone.

Other Efficacy Variables

The fresh plant 20-mg tablets produced a statistically significant and clinically relevant prolongation of the calf-refilling rate to considerably longer than the 25 seconds considered to be the lower threshold of the normal range. Unlike placebo, the active treatment restored functionality of the vein wall.

Safety

These 4 studies testify to the excellent safety profile of HCSE-containing preparations. The total treated population of 219 reported only 8 adverse events—all gastrointestinal—that were considered probably or possibly related to any of the formulations. Nausea is a well-documented adverse effect of aescin, and the low incidence of it in these studies indicates that the film coating renders the tablets resistant to gastric acid.

CONCLUSION

The efficacy of horse chestnut seed extract is well founded and comparable with that of standard compression therapy. Of the available HCSE preparations, Aesculaforce formulations are among the best researched in clinical trials that complied with stringent regulatory requirements. Considered together, these studies show that the fresh plant HCSE products investigated here, whether taken orally or applied topically, provide effective treatment for patients with stage I and II chronic venous insufficiency, as assessed by both objective and subjective methods. Safe, well tolerated, and acceptable to patients, the fresh plant HCSE preparation Aesculaforce represents a real alternative therapy for those with mild to moderate forms of venous insufficiency.

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