D. Shah
Silvia Bommer
F. H. Degenring

Aesculaforce in chronic venous insufficiency

Placebo-controlled double-blind study to demonstrate the efficacy and tolerability of a plant remedy

The Aesculaforce vein tablets investigated in the present study contain a dried extract obtained from the fresh seeds of the horse chestnut (HCE) standardised to 20 mg aescin and also standardised through the use of mixed annual batches and by plant provenance. HCE preparations diminish the activity of lysosomal enzymes associated with chronic venous insufficiency (CVI) and thus reduce the breakdown of mucopolysaccharide (glycocalyx) in the capillary wall. They enhance capillary resistance, improve membrane-sealing and also have a venotonic effect. In a multi-centre, placebo-controlled study, 30 patients each with Widmer stage I or II CVI were randomized to 6 weeks of daily treatment with either 3 × 2 tablets of the test substance, or the same number of placebo tablets having an identical appearance and taste. With regard to the very good tolerability – presumably not least on account of the stomach-protecting film coating of the tablets – no differences were found in comparison with placebo. With respect to efficacy, in contrast, there was a statistically significant difference in terms of the time course of the reduction in ankle oedema and venous filling rate that favoured the test substance. With respect to the improvement in the subjective symptoms, however, there was only a small, statistically non-significant difference favouring the test substances, since the initial effect of medical care under placebo, in particular in Widmer stage I patients, also observed in other therapeutic studies – admittedly only half as long – of patients with this venous disease, persisted until the end of treatment.

In all civilized countries, there is a high prevalence of venous circulatory disorders in the adult population. As a result of valvular incompetence, due usually to inflammation or venous occlusion, this disease is characterised by venous stasis. The associated increase in the filtration of fluid and electrolytes, as well as low-molecular weight proteins, into the tissue interstitium, promotes the formation of oedema in the calf and at the ankles that is typical of the Widmer stage I of chronic venous insufficiency (CVI).

In addition to weight reduction and the use of compression bandages, preparations containing horse chestnut extract (HCE) have long been used in the treatment of venous circulatory disorders The efficacy of such preparations is due to their action in reducing vessel wall permeability Clinically, this mechanism of action can be objectified by the improvement in, or elimination of, oedema in the calf and at the ankles. Subjectively, an amelioration or even elimination of such typical complaints as a sensation of heaviness or tension, pain and a burning sensation or itching and paraesthesias affecting the legs is experienced.

The extent to which the skin alterations occurring in Widmer stage II disease, such as hyperpigmentation, eczema and/or induration, can be reduced or even eliminated by HCE preparations, has to date not been investigated. The verification of such effects, as a consequence of successful treatment of the oedema, would be possible only in a long-term therapeutic study involving a large number of patients. Widmer stage III CVI is not an indication for primary oral treatment with HCE preparations when florid ulceration of the leg is pre-

sent. Since it would not appear ethically justifiable to treat this clinical picture with placebo, the present controlled study was limited to Widmer stage I and stage II CVI.

As confirmatory target parameters, ankle circumference and the summed score of the specific complaints were selected. As an addition descriptive variable for efficacy, the rate of venous filling after repositioning the legs from the recumbent to the dependent position was employed. Tolerability was assessed on the basis of the frequency of occurrence of undesired events.

Parameter	Score für Parameter
Heavy, tired legs/sensation of tension	0 = not present
Pain in the legs	1 = mild
Itching	2 = moderate
Paraesthesias	3 = appreciable
	4 = pronounced
	5 = very pronounced

Table 1: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Criteria for the assessment of the symptoms prior to the start of the study.

Treatment	Age [years]	Height [cm]	Weight [kg]	n
Placebo	56 ± 11	166 ± 7	75 ± 15	30
Test substance	54 ± 12	166 ± 6	75 ± 10	30

Table 2: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Demographic data of the participants.

Material and method

The *Aesculus* extract was obtained using 60 % m/m ethanol as extraction medium. The tablets, coated with a film resistant to gastric acid to protect the gastric mucosa, each contained 63–90 mg of native extract, equivalent to 20.0 mg in the form of triterpene glycoside calculated as anhydrous aescin. The daily dosage was 3 × 2 tablets, giving a total of 120 mg aescin, and thus corresponded approximately to the daily dose of 100 mg aescin in retard form given in two daily doses as recommended by the processing monograph of the Commission E in Germany (BAnz No. 71. 18.4.1994).

Initially, a general practitioner and an angiologist in Germany agreed to participate in the placebo-controlled double-blind study that was conducted between the end of March 1995 and the beginning of September 1996. For technical reasons, however, the latter was unable to recruit patients to the study and had to be replaced by two phlebologists, each of whom recruited one-half of the 30 patients originally scheduled for each test centre.

Inclusion criteria included a minimum age of 18 years and Widmer stage I or II CVI, with an admission summed score and a symptoms summed score of at least 6. The admission summed score comprised a 6-grade medical assessment of the three diagnostic criteria: oedema, skin pigmentation and eczema. The symptoms summed score was also calculated on the basis of a 6-grade medical assessment of the symptoms: sensation of heaviness or tension, pain, burning sensation, itching and paraesthesias affecting the legs **(Table 1)**.

The 60 patients who met these criteria and gave their written informed consent to participate in the study were made up of 4 men and 56 women **(Table 2)**. After the examination on admission, an interim follow-up was carried out after 2, and a final follow-up after 6, weeks.

As the primary target parameter, the circumference of the more severely affected leg, measured immediately above the ankle, was selected. The second target parameter was the summed score of the above-mentioned subjective symptoms in the legs. As the statistical working hypothesis, a significant decrease in ankle circumference and/or in the summed score of the subjective symptoms in the test substance group as compared with the placebo group was established. The merely descriptive additional parameter of venous filling, as an indication of the position-dependent capacity of the blood vessels, was determined by plethysmography. For this purpose, the time required to achieve maximum volume increase was determined by having the patient dangle his legs after first elevating them for 15 minutes at an angle of 45° to empty them of blood.

To investigate tolerability, any undesired events experienced by the patient during the study, were recorded. With the agreement of the ethics commission, no laboratory investigations were carried out, since – as was shown by toxicity data – there is no risk of organic functional changes associated with the use of HCE.

Treatment	Abandoned after	Event	Causal relationship
Placebo	7 days	gastric upset	probable
Placebo	8 days	acute gastric complaints	probable
Placebo	21 days	acute thrombophlebitis	questionable or unlikely
Test substance	2 days	heart pains	questionable or unlikely
Test substance	7 days	acute gastric complaints with abdominal cramps	possible
Test substance	28 days	intercurrent urinary tract infection	improbable

Table 3: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Adverse reactions occurring during the study.

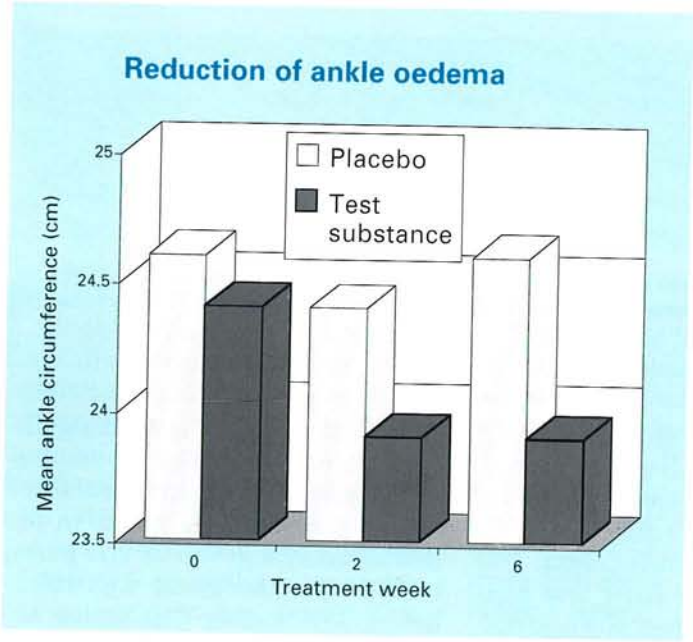

Figure 1: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Reduction of ankle oedema over time.

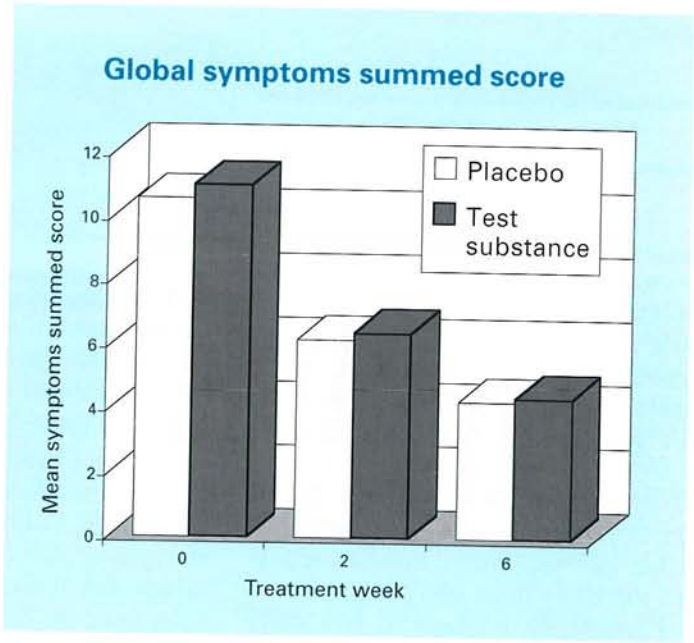

Figure 2: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Global symptoms summed score.

The statistical analysis took the form of a two-factorial variance analysis (Friedman test) at a significance level of 0.05. For this purpose, the venous filling data had to be transformed in order to meet the prerequisites for normal distribution and variance homogeneity.

Results

The data of 52 patients were admitted to the final evaluation. Nine patients abandoned treatment, one of whom was replaced, since, citing loss of interest, he left the study in the first days of treatment. Two further patients were removed from the study after the first follow-up, on account of non-compliance, and were not replaced. Of the remaining 6 dropouts, three each in the test substance and placebo groups cited «adverse reactions» as the reason for leaving the study **(Table 3)**.

Compliance with tablet use was checked for each patient at the end of the 6-week period of treatment by counting the remaining tablets; in none of the patients was compliance assessed to be negative.

Measurement of leg circumference at the level of the ankle, the primary target parameter and objectifiable finding, revealed a statistically significant difference in the time course of oedema reduction ($F_{group \times time} = 3.144$; $p<0.05$) **(Figure 1)**, which remained unchanged after 6-weeks of treatment with placebo, but decreased by 0.5 cm in the test substance group.

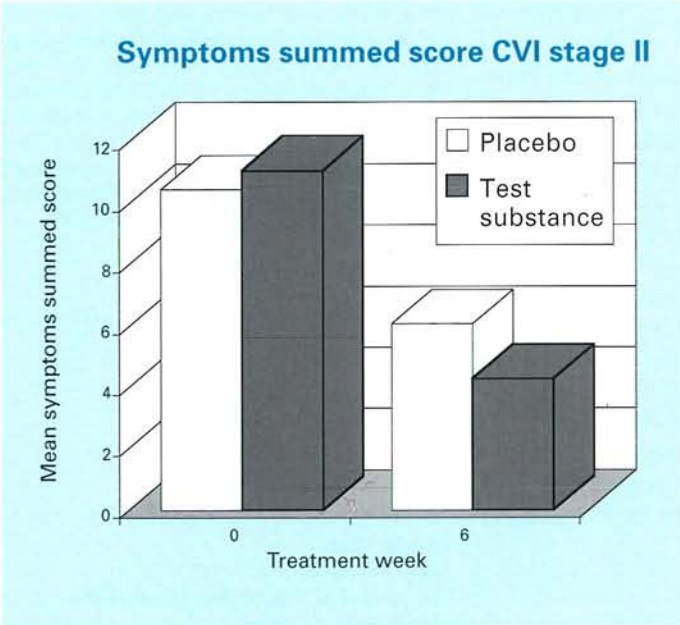

Figure 3: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Symptoms summed score over time in patients with stage II CVI.

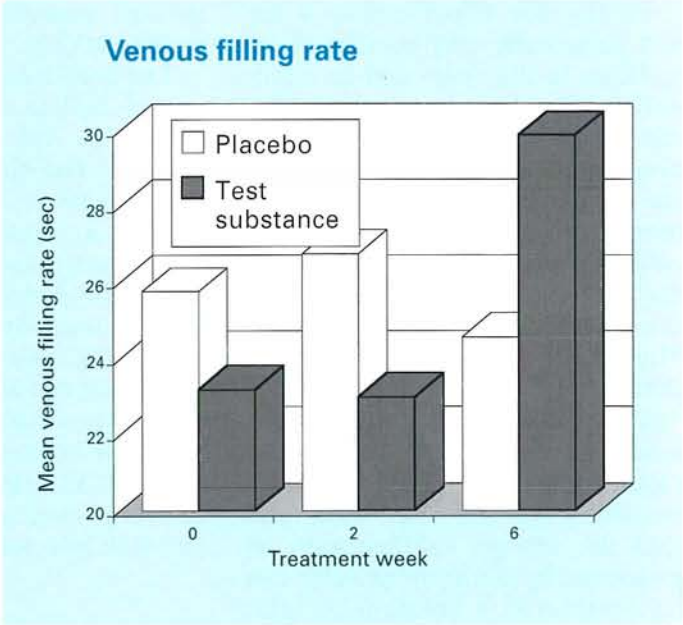

Figure 4: Placebo-controlled double-blind study in patients with chronic venous insufficiency: Treatment with Aesculaforce vein tablets for 6 weeks. Venous filling rate.

The summed score of the subjective symptoms, the second target parameter, decreased highly significantly both in the test substance and placebo groups (F_{time} = 142.12; $p<0.0001$) **(Figure 2)**. However, the time course of the improvement in symptoms showed no significant difference between the groups ($F_{group \times time}$ = 0.115, p=0.89). A subsequent evaluation with account being taken of the two Widmer grades of severity of CVI, however, showed that, in the case of the more severely afflicted stage II patients, statistical significance favouring the test substance vis-à-vis placebo, was only just missed ($F_{group \times time}$ = 3.091; P_{one} = 0.0511) **(Figure 3)**.

Digital venous or photoplethysmographic measurement of the refilling rate in the calf, used as an addition parameter, also proved very meaningful, favouring the Aesculaforce vein tablets ($F_{group \times time}$ = 3.661, p=0.0308) with an increase from 23 to 30 seconds for the test substance, but no change for placebo **(Figure 4)**.

To investigate tolerability, both physicians and patients were requested, at the end of the trial, to make separate global assessments in the form of a score. The assessment revealed no statistical differences. The mean values were identical for both physicians and patients, being 1.32 in the placebo, and 1.38 in the test substance, group.

Clinical evaluation and discussion

The target parameter selected for objectification of the results of treatment was ankle oedema, which is present in all stages of CVI. Despite the relative inaccuracy of measurements with a tape measure in comparison with a water plethysmometer – which did not form part of the equipment normally available in the study centres – this approach was accepted, since it is long-standing examination practice at those centres.

Already after two weeks of treatment with the Aesculaforce vein tablets, a clinically relevant reduction in ankle circumference was observed in the test substance group. No further reduction in ankle circumference was observed during the remaining time to the end of treatment – presumably because virtually complete elimination of oedema had already been achieved after the first two weeks. Thus, the efficacy of the film-coated Aesculaforce vein tablets can be considered equal to the capacity for reducing tissue fluid reported for other non-enteric coated Aesculus or HCE preparations available in tablet form.

In most published studies of CVI treatment with HCE, an improvement in the illness-specific symptoms was also seen with placebo. This is explained by the extremely pronounced psychological effect of medical care on patients with this disease. In the present study, this «initial effect» seen with placebo and of equal magnitude to that observed with the test substance, continued to increase until the end of treatment after 42 days. The data currently available suggest that this effect is correlated inversely with the severity of the venous disease.

Finally, the effectiveness of the test substance was confirmed, in addition to the reduction or elimination of ankle oedema, also by the clinically relevant increase in position-dependent venous capacity in the test substance group, which manifested as a prolongation of the refilling rate to considerably above the 25 seconds considered to be the lower threshold of normalcy. These results allow us to conclude that 6 weeks of treatment with Aesculaforce vein tablets, in contrast to placebo, results in the restoration of virtually full functionability of the vein wall, and that the venous refilling rate as measured by plethysmography, can be considered a suitable complementary target parameter for determining the position-dependent venous capacity in therapeutic studies of CVI.

The good tolerability of the film-coated tablets was expected, and was in no way inferior to that of placebo. The single case in which the care-providing physician considered a causal relationship between gastric complaints and treatment with Aesculaforce to be possible, is unlikely to be attributable to the HCE, since the enteric coating allows release of the substance only in the small bowel.

Thus, the oedema-protective treatment of CVI with Aesculaforce vein tablets proved to be both effective and well tolerated.

The study was carried out with the help of Dr. med. M. Dorn, Scientific Counselling, Elz, by the practising physicians Dr. med. B. Wildenhues, general practitioner, Limburg, Dr. med. D. Kubelka, phlebologist, Koblenz, and Dr. med. U. Kamphausen, surgeon and phlebologist, Mönchengladbach. Statistical planning and evaluation was the responsibility of Dr. Franzen, Wissoft, Marburg.

References may be requested from the author.

Address correspondence to:

Deryk Shah
Silvia Bommer
Dr. med. F.H. Degenring, Head of the Medical Department
Bioforce AG
CH-9325 Roggwil