HR, 0-(Beta-Hydroxyethyl)-Rutosides, in Comparison with Diosmin+Hesperidin in Chronic Venous Insufficiency and Venous Microangiopathy: An Independent, Prospective, Comparative Registry Study

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The aim of this independent study was to investigate differences in efficacy between HR, (0-[beta-hydroxyethyl]-rutosides) and D+H (500 mg, diosmin+hesperidin) in patients with chronic venous insufficiency (CVI). A first group of 90 patients with severe venous hypertension (CVI, ankle swelling) were randomized into an HR or a D+H group. The HR group received oral HR (2 g/day, 8 weeks); the D+H group received a 500 mg tablet 3 times daily for 8 weeks. A second group of comparable patients was included in a registry following the same study format. Patients were openly included; the 2 treatments were administered with the same methods and procedures. Clinical conditions were comparable to those described in the randomized study. Patients treated for at least 8 weeks were included in the registry. A number of physicians (specialists or general practitioners) included patients when they considered that clinical conditions were compatible with using 1 of the 2 treatments on the basis of their personal evaluation and experience. When cases were compatible with the registry, the prescribing physician communicated the case. Patients were evaluated without interfering with the treatment. Main targets of evaluation were skin flux at rest (RF), strain-gauge-derived rate of ankle swelling (RAS), and analogue symptoms score (ASLS). Ninety subjects completed the study in the first group; 122 in the second, registry group (total of 212 patients). The first and second (registry) groups and the 2 treatment groups were comparable for age and sex distribution. The pooled mean age was 42 years (SD ±5.5) in the HR group (46+62 patients) and 41.5 (SD ±6) in the D+H group (44+60 patients). Considering pooled data there were no differences in microcirculatory parameters between the pooled treatment groups at inclusion. A significant decrease ($p<0.05$) in RF and RAS was observed in the HR group at 8 weeks. The decrease in resting skin flux and in capillary filtration was associated with a significant improvement in signs/symptoms (analogue scale line) from an average of 9.4 (range 3–10) to

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3.3 (4–6) ($p < 0.05$). Significantly smaller variations were observed in the D+H group. The decrease in RF was 47.6% in the HR group vs 15.7% in the D+H group. The decrease in RAS was 40.9% in the HR group vs 12.8% in the D+H group. The decrease in ASLS was 64.8% in the HR group vs 12.9% in the comparative group. In conclusion venous microangiopathy and edema were improved by the treatment with HR both in the randomized study and in the pooled analysis. The comparison with D+H indicates that HR is comparatively more effective both on microcirculatory parameters and on signs/symptoms of CVI.

Introduction

HR (Venoruton® or Paroven®; 0-[beta-hydroxyethyl]-rutosides) has been used to treat chronic venous insufficiency and signs/symptoms associated with varicose veins and deep venous disease. Several studies have reported symptomatic relief and a decreased capillary filtration after the administration of the oral preparations.[1-3] The evolution of new microcirculatory methods[4] permits study, in a quantitative way, of microcirculatory changes produced by pharmacologic treatment at the areas affected by chronic venous disease and microangiopathy.[5-13]

The effects of treatments of edema and microcirculatory changes associated with chronic venous hypertension (CVH) can be evaluated by dynamic microcirculatory parameters and dynamic capillary responses, ie, the venoarteriolar response (VAR), through noninvasive tests such as laser Doppler flowmetry (LDF).[11-14] In subjects with venous microangiopathy the skin flux at rest in the perimalleolar region (RF) is increased; the VAR (namely, the vasoconstriction measured on standing) is altered and other microcirculatory changes are present (PO_2 is decreased, PCO_2 is increased, and capillary filtration, visible as edema, is greatly increased).[4-14]

To evaluate how oral HR[1-3] was effective in comparison with the combination micronized diosmin + hesperidin (D + H), a first study was perfomed. This was an independent, prospective, controlled, and randomized trial, followed by a second trial: a registry study. This combination D + H is also used to control signs and symptoms of venous insufficiency.[15] The results of the first, randomized, trial have already been separately published.[16]

Materials and Methods

Inclusion Criteria

Evaluation methods for chronic venous insufficiency (CVI) described in this article have been reported in detail in previous publications.[10-14,16] In the first part of this study 90 patients with severe chronic venous hypertension, with ambulatory venous pressure (AVP) > 60 mm Hg and refilling time (RT) < 8 seconds),[3,4] associated with ankle swelling and lipodermatosclerosis, were included after a washout period of 2 weeks.

Exclusion Criteria

No other cardiovascular disease was present. Diabetic patients and those with bone or joint disorders and any systemic disease requiring medical treatment were also excluded. We excluded, with the use of ultrasound, the presence of recent thrombosis (12 months). Patients with a history of thrombosis in the previous 24 months were also excluded.

Noninvasive Investigations

Venous reflux in the popliteal vein was shown by color duplex; the increase in venous pressure was measured by AVP. AVP was significantly increased[3,4] in all patients at inclusion (AVP was higher than 60 mm Hg in all included limbs owing to combined superficial and deep, venous incompetence). AVP values after exercise were not normalized by a tourniquet excluding the superficial venous system (this indicated combined, superficial and deep, venous incompetence). Superficial venous incompetence in all studied

limbs was associated with deep venous incompetence (most of venous hypertension was due to deep incompetence).

Treatment

The combined database (randomized study+registry study): in the first part of the study, after inclusion and informed consent, patients were randomized into a Venoruton® or D+H group. Patients in the Venoruton® group received 1 g sachet, twice daily, for 8 weeks; patients in the D+H group received a 500 mg tablet (Daflon® 500) 3 times daily.[16]

In the second part of the study a registry was created. Patients were included openly and the 2 treatment schemes were administered with the same methods, procedures, and protocol. Patients treated for at least 8 weeks were included in the registry and reevaluated at 8 weeks.

For this registry study a number of physicians (specialists or general practitioners) included subjects, when they considered that the clinical conditions were comparable to those described in the registry, using 1 of the 2 treatments on the basis of their personal evaluation and experience. To include the data into the registry, the treatment was to be used for at least 8 weeks. Therefore, subjects treated for a shorter period of time were excluded. When patients and treatment were compatible with the registry, the prescribing physician communicated the case. The subjects were evaluated without interfering with the treatment.

Measurements

All measurements were made in a room at constant temperature (21°C) before 10 am to avoid the effect of standing, and after 30 minutes of acclimatization in a resting, supine position. LDF (laser Doppler flowmetry), resting flux (RF), namely, the skin flux in the supine resting position, and capillary filtration, measured as the rate of ankle swelling (RAS) by strain-gauge plethysmography (Hokanson, USA), were measured at inclusion and repeated after 8 weeks of treatment. A TSI-Vasamedics laser Doppler flowmeter (TSI, St Paul, USA) was used to measure skin flux at the internal perimalleolar region—the area mostly affected by venous hypertension and microangiopathy, and often a frequent localization of ulcerations in patients with CVH. All methods used were in accord with the methods described in detail in previous publications.[3-4,14]

A composite, analogue clinical score based on signs and symptoms (edema, pain, restless limbs, subjective swelling, skin alterations/redness) and ranging between 1 and 10 was recorded by patients—after careful briefing and teaching them its meaning—at inclusion and after 8 weeks of treatment by marking on an analogue scale line the level of discomfort (Figure 1).

In the first part of the study routine blood tests were made at the beginning of the study and after 8 weeks. In the registry study blood tests were not monitored.

Total analogue scale line score (ASLS).

0==========X==========10

Score Composition	Score
1. Edema	0–2
2. Pain	0–2
3. Restless limbs	0–2
4. Subjective swelling	0–2
5. Skin alterations/redness	0–2
Total	0–10

Figure 1.
A composite analogue score (based on signs/symptoms: edema, pain, restless limbs, subjective swelling, skin alterations/redness) ranging from 1 to 10 was considered and evaluated by patients at inclusion and after the 8 weeks of treatment by marking on the analogue scale line the level of discomfort. Patients indicated a value for each item (0 = no symptom; 1 = symptom present, not continuously; 2 = symptom severe, continuous).

Statistical Analysis

Statistical analysis was performed with the Mann-Whitney U-test and the Chi-squared test. The proportions of included samples in the 2 groups were calculated in groups of at least 60 patients in each treatment group (2-tailed test) to detect significant variations in the microcirculatory measurements before and after—and differences between treatment groups at 8 weeks. It was considered that 10% variations in most microcirculatory measurements are possible as a consequence of spontaneous variations in the capillary system even under standardized conditions. Therefore, an arbitrary cut-off point of at least a >15% variation in parameters was considered to be valid to define changes due to treatment (considering that 95% of variations in parameter values in standard environment and conditions are below 12%).

Results

Details of the 2 groups (the randomized study and the registry group) are shown in Table I. The pooled mean age of the patients completing the overall study was 42 years (SD ±5.5) in the Venoruton® group (46+62 patients) and 41.7 (SD ±8) in the D+H group (44+60 patients).

Dropouts

The registry study: 143 included patients; 21 were lost (11 in D+H group vs 10 in the Venoruton® group) with 122 completing the study (62 Venoruton®, 60 D+H). No subject was lost for side effects or clinical problems. They all failed to follow the protocol or did not come to the control evaluation for nonmedical reasons. Seven patients decided to have invasive treatment (5 sclerotherapy, 2 in the Venoruton® and 3 in the D+H group, and 2 had localized vein surgery, 1 in each group).

There were no significant differences between the HR and D+H treatment groups at inclusion considering microcirculatory parameters, sex, age distribution, and clinical characteristics. The variations in microcirculatory measurements are shown in Table II for both studies.

A significant decrease ($p < 0.05$) in RF and RAS was observed in the HR group at 8 weeks, both in the second, registry study (Table II) and in the pooled results (Table III, Figures 2, 3).

Also, both in the second study and in the pooled results the decrease in resting skin flux and in capillary filtration was associated with a significant improvement in signs and symptoms in the HR group as shown with the pooled analogue scale line score (ASLS) from an average of 9.4 (range 3–10) at inclusion to 3.3 (range 4–6) vs 9.3 (3–10) at inclusion in the D+H

Table I. Details of the two treatment groups.

	Number of Patients	Age	M:F	AVP	RT
Randomized study					
Total included	90				
HR group	46	41 (5)	25:21	69.3 (4)	6.7 (3)
D+H group	44	41.4 (5)	23:21	68.3 (3)	6.5 (3)
Registry study					
Total included	122				
HR group	62	43 (6)	33:29	68 (6)	6 (2)
D+H group	60	42 (7)	28:32	67 (5)	6.2 (3)

AVP = ambulatory venous pressure; RT = refilling time; SD (standard deviation, in brackets).

Table II. Variations in resting flux, rate of ankle swelling, and analogue scale line score (mean and standard deviation) before and after 8 weeks in the HR and D+H groups.

	Baseline	8 weeks	Percent Variation
Data from the randomized study 1:			
HR			
RF, flux units	1.78 ±0.2	1.11 ±0.2*	37*
RAS, mL/minute per 100 mL	2.33 ±0.1	1.31 ±0.1*	43*
ASLS, mean (range)	9.6 (2–10)	3.1 (4–8)*	67.7*
D+H			
RF, flux units	1.77 ±0.2	1.69 ±0.2†	4.5†
RAS, mL/minute per 100 mL	2.31 ±0.2	2.21 ±0.1†	4.4†
ASLS, mean (range)	9.5 (2–10)	8.9 (3–10)†	0.6†
Data from the registry study 2:			
HR			
RF, flux units	2.42 ±0.1	1.1 ±0.1*	54.5*
RAS, mL/minute per 100 mL	2.07 ±0.1	1.3 ±0.1*	37.1*
ASLS, mean (range)	9.2 (3–8)	3.5 (3–5)*	61.9*
D+H			
RF, flux units	2.03 ±0.1	1.5 ±0.1†	26.1†
RAS, mL/minute per 100 mL	1.91 ±0.1	1.47 ±0.1†	23†
ASLS, mean (range)	9.1 (4–8)	7.3 (3–8)†	19.7†

*$p < 0.05$ difference before-after; †$p < 0.05$, difference between groups.
ASLS = analogue scale line score (0–10).

Table III. Pooled data: Study 1 and study 2. Variations in resting flux (RF), rate of ankle swelling (RAS), and analogue scale line score (mean and standard deviation) before and after 8 weeks in the HR and D+H groups.

	Baseline	8 weeks	Percent Variation
HR			
RF, flux units	2.1 ±0.2	1.1 ±0.1*	47.6*
RAS, mL/minute per 100 mL	2.2 ±0.2	1.3 ±0.2*	40.9*
ASLS, mean (range)	9.4 (3–10)	3.3 (4–6)*	64.8*
D+H			
RF, flux units	1.9 ±0.1	1.6 ±0.2†	15.7†
RAS, mL/minute per 100 mL	2.11 ±0.1	1.84 ±0.2†	12.8†
ASLS, mean (range)	9.3 (3–10)	8.1 (3–10)†	12.9†

*$p < 0.05$ difference before-after; †$p < 0.05$ difference between groups.
ASLS = analogue scale line score (0–10). This table includes both the first treatment group (published study) and the registry group.

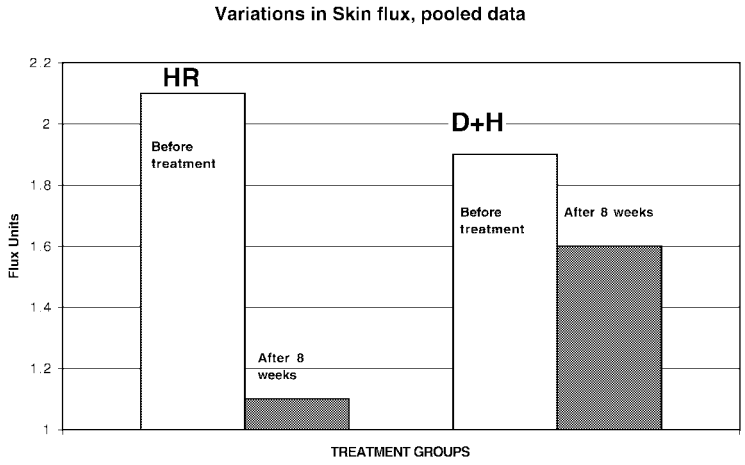

Figure 2.
Pooled data: Variations in skin flux in the 2 groups.

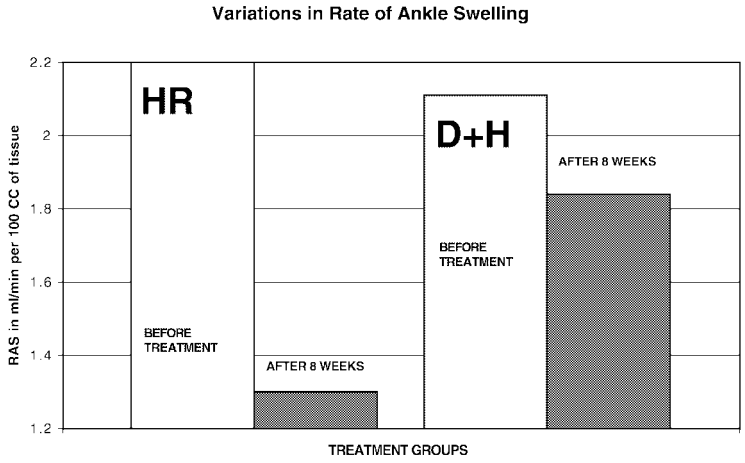

Figure 3.
Pooled data: Variations in the rate of ankle swelling.

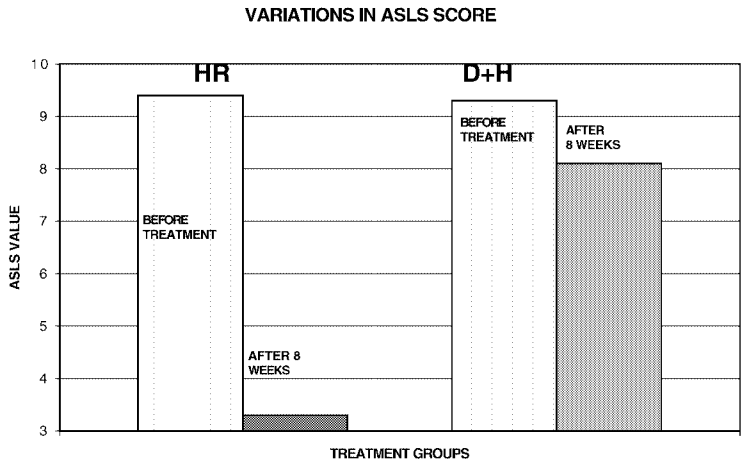

Figure 4.
Pooled data: Variations in analogue (ASLS) score.

group to 8.1 (3–10) at 8 weeks (ns) (Table III) (Figure 4).

Significantly smaller variations in microcirculation parameters were observed in the D+H group. The decrease in RF was 47.6% in the HR group vs 15.7% in the D+H group. The decrease in RAS was 40.9% in the HR group vs 12.8% in the D+H group (Table III). The decrease in ASLS was 64.8% in the HR group vs 12.9% in the D+H group (Table III).

Safety

No side effects due to treatment were observed. Compliance and tolerability were very good (no patient had to stop treatment and there were no dropouts due to side effects).

Discussion

The effects of Venoruton® on skin flux at rest, ankle swelling, and capillary filtration could be observed even in a limited sample of patients after 8 weeks of treatment. The decrease in capillary filtration and edema were associated with symptomatic improvement as observed in previous reports.[1,2] The comparison with D+H in the treatment of CVI indicates a higher level of efficacy of HR when considering these parameters.

Microcirculatory methods are useful to quantify and follow up the evolution of venous hypertensive microangiopathy and the effects of treatments[10-14] on the microcirculation. Venous ulceration and CVI are always associated with important microcirculatory changes.[17-20] The alterations in skin flux and other microcirculatory dynamic parameters[21,22] are important quantitative measurements in the evaluation of venous microangiopathy associated with the development of edema. The quantitative evaluation of capillary filtration is relatively complex but very effective in defining the degree of venous microangiopathy[23] and its changes in time with treatment, for an increased capillary filtration, clinically present as edema, is the most important, often the single, initial sign present in CVI.

The pooled data from these 2 independent studies indicate that oral treatment with HR is very effective and rapid in improving the microcirculation in patients with CVI and venous microangiopathy characterized by high skin flux, high RAS, and edema in the perimalleolar region. At least 76% of patients with chronic venous insufficiency and disease had measurable evidence of alterations in the parameters evaluated in this study.

In the present studies the effects of D+H in CVH were limited. Clinical results from previous studies[15,24,25] indicate efficacy but were not evaluating the same microcirculatory parameters.

The definitive treatment of CVH is usually compression and surgery and/or sclerotherapy if possible.[3] However, in most patients, medical and conservative measures are effective and may also be used in association with interventional (surgery, sclerotherapy) methods. Treatment with HR is effective and should be available in these conditions, particularly when edema is significant.

Recent randomized controlled studies[26-29] have shown the efficacy of HR in CVH on the microcirculation and on different biochemical parameters, including plasma free-radicals.[30] HR is safe, is very well tolerated, and has been prescribed for several years. New applications (ie, flight edema and microangiopathy) are important indications both for normal subjects prone to edema and patients with venous disease. Edema present in diabetics may be controlled with HR.[27] A recent randomized study and meta-analysis indicates the general efficacy and safety of HR.[31] The specific affinity of hydroxyethyl-rutosides for the venous wall components and its efficacy in preventing early occlusion of aortocoronary vein grafts has been also reported.[32] HR is effective on blood elements linked to inflammation and affecting the endothelium and appears to prevent the chronic alterations found in severe venous insufficiency.[33,34]

In conclusion this study confirms the clinical efficacy of HR in comparison with D+H in chronic venous insufficiency and venous microangiopathy. The study indicates the important role of HR in the treatment and control of this common clinical problem.

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