A double blind, randomized study evaluating the influence of semi-synthetic diosmin, and a purified, micronized flavonoid fraction (diosmin and hesperidin), on symptoms of chronic venous insufficiency of the lower limb – a four-week observation.

Introduction

Lower limb ailments such as: leg heaviness, pain or swelling are periodically present in 30% of women. Long periods of standing or sitting as well as the high temperature of a given environment intensify these problems. Most often they refer to chronic venous insufficiency [1]. For over 30 years flavonoids have been used in the symptomatic treatment of venous insufficiency. In the 1980s of the 20th century the clinical effectiveness of one of natural flavonoids - diosmin was defined, which was followed later by the efficacy of semi-synthetic diosmin [3,4]. Semi-synthetic diosmin is a substance used since 1987. In 2002 it was described for the first time in the European Pharmacopoeia [4]. Specimens available on the market contain either a fraction of diosmin with hesperidin or pure semi-synthetic diosmin. Some specimens - e.g. in the reference drug used in this study, contain a purified and micronized flavonoid fraction of diosmin with hesperidin. Micronization, as it has been proved, improves absorption of the flavonoids from the galenic form of the specimen [5,6].

AIM OF THE STUDY

The aim of the study was a comparison of the clinical effectiveness of semi-synthetic diosmin with a drug containing a purified, micronized flavonoid fraction of diosmin and hesperidin in women with symptoms of chronic venous insufficiency of the lower limbs.

MATERIAL AND METHODS

The study was a randomized, multi-center, double blind trial with the use of the *double-dummy* technique. Appropriate Ethics Boards have granted permits for the study and thus it has been registered at the Central Register of Clinical Trials, under

entry number 312 / 02. It was carried-out in the period from October 2002 to February 2003 at three medical centers: Department of Surgery, Oncology and Vascular Diseases of the Military Medical Institute, Warsaw, Department of General Surgery of the Hospital of the Ministry of Home Affairs and Administration, Warsaw and in the Department of Vascular Surgery and Angiology, The 'Bielański' Hospital, Warsaw.

The study included women in the age range between 20 and 60 years with symptoms of chronic venous insufficiency in stage 0 to 3 according to CEAP classification, indicating: 0 – invisible and impalpable changes, 1 –telangiectasia and reticular veins, 2 – varices (not subjected to surgery during last 6 months preceding the study and not requiring surgical treatment within the 3 months which followed the inclusion in the study), 3 – swelling with no skin changes.

Patients did not take phlebotropic drugs, nicotine acid derivatives, pentoxiphylline or other drugs, which could potentially affect the function of the veins or painkillers except for the temporary use of paracetamol within the period of at least 30 days prior to the inclusion of a patient for the study. During the first (baseline) visit (V1) the intensity of ailments was assessed according to a visual grading scale consisting of 30 points. Attaining of at least 6 points in the above-described scale was the criterion enabling the inclusion into the study. Prior to his or her participation in the study each patient had signed an informed consent form. Patients with a history of intolerance to diosmin, with neuropathy, lower limb ischaemia, lower limb ulcerations, symptoms of lower limb, osteoarticular system degenerative disease, symptoms of cardiac-related circulatory insufficiency or lower limb injury in the 6 month period prior to the study have been excluded from the study. During the study the patients did not use any compression therapy products. Pregnant or breast-feeding women as well as those requiring vasoactive drug therapy, diuretic drugs, painkillers, anti-inflammatory or other drugs which may have an affect on the veins have also been excluded from the study. All patients who met the above described inclusion criteria were randomly assigned to Group A – in which semi-synthetic diosmin was administered (in a dose of one 600 mg capsule of diosmin in the morning and 1 placebo capsule in the evening) or to Group B – receiving a purified, micronized flavonoid fraction of diosmin with hesperidin (450 mg / 50 mg), twice a day, once in the morning and once in the evening. The scheme of the study is presented in Figure 1.

Patients included in the study underwent two visits: the first (baseline) visit (V1) and a check-up visit (V2), after 28 days of treatment, and every week they filled out an individual drug effectiveness assessment questionnaire. In the course of the visit the investigating physician interviewed the patients, carried out a full medical examination (including blood pressure, heart rate, radial and dorsalis pedis artery pulse) taking into account the symptoms of venous insufficiency and measuring the circumference of both calves at the level of 10 and 30 cm above the ankle.

Moreover, during the check-up visit the physician assessed the influence of the administered drugs using the scale from 0 to 5 points.

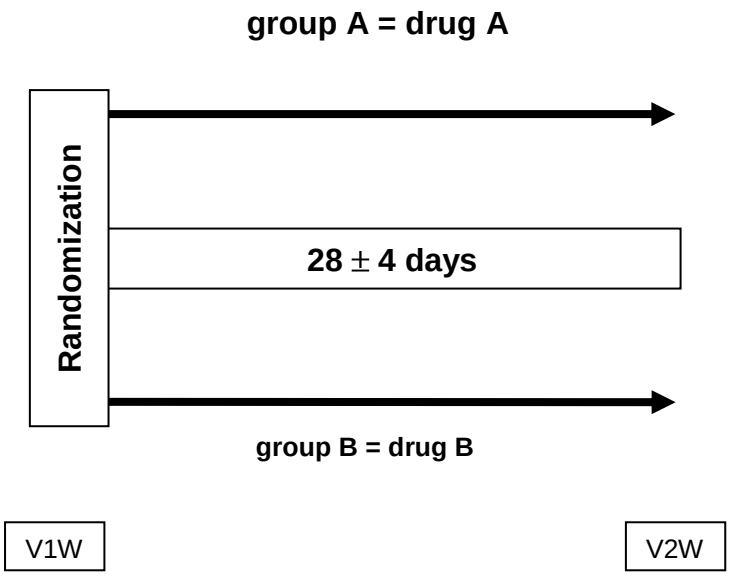

Figure 1: the scheme of the study. Drug A = Otrex® 600 (Schwarz Pharma/ Stragen Pharma), Drug B = Detralex® (Servier).

The primary variable in the study was the self-assessment of the therapy effectiveness, carried out by patients with the use of a questionnaire, which was based on a visual scale of lower limb ailment intensity. The self-assessment questionnaire consisted of 6 questions concerning: swelling, sensation of “heaviness” of the legs and lower limb fatigue, “heat in the legs”, night muscle cramps and pain. Ailment intensity estimated on the scale of 0 to 5 points was recorded from the first day of active therapy, on a weekly basis, until the last day of the study [day 0 (D0=V1), day 7 (D7), day 14 (D14), day 21 (D21), day 28 (D28)].

A total score of at least 6 points from the answers to all the questions during the initial evaluation (D0=V1) has been estimated as the criterion for inclusion in the study. The main variable was the total score from all the answers to all the questions from the questionnaire. Individual analyses of each of the 6 questions from the questionnaire have also been carried out.

A statistical analysis has been carried out with the use of the Statistica v. 6.0. package. The statistical change of group diversity and the relations between the features tested were assessed on **α** =0.05 level, on the basis of **β** =0.8 tests.

The comparison of average values and average changes over time for each of the six scales in the self-assessment questionnaire and the total number of points of the questionnaire between therapy groups A and B was made on the basis of the Mann-Whitney 'U' Test at each time point. The significance of changes over time defined as an increase of the scale referring to self-assessment at the initial point in each therapy group was measured with a non-parametric paired test. Comparison of average calf circumferences and their changes over time in the group taking drug A in comparison with the group treated with drug B was made according to Dunnett's test, whereas the significance of the calf circumferences of each group was evaluated on the basis of the t-Student test for bonded pairs.

In order to verify the hypothesis concerning equal frequencies of abnormality in the vessels and other systems at the beginning of (V1) and at the end of study (V2), McNemar's test was conducted separately for each group [2].

The safety analysis included all patients who had taken at least one dose of the tested drugs (n=126).

	Group A	Group B	p between A and B
Number of patients	60 (50%)	59 (50%)	
Age (years)	45 ± 10	45 ± 10	0.8352
Height (cm)	164 ± 6	164 ± 7	0.9095
Weight (kg)	68 ± 10	68 ± 11	0.7939
Number of patients of reproductive age	57 (95%)	57 (97%)	0.662
Number of patients using contraceptives	4 (7%)	7 (12%)	0.208
Number of patients who smoke cigarettes	16 (27%)	18 (31%)	0.643
Number of patients with secondary or university education	54 (90%)	50 (85%)	0.388
Number of patients with additional ailments at the beginning of study	29(48%)	33 (56%)	0.407
Number of patients with inherited susceptibility to a disease in their history	39 (65%)	43 (73%)	0.353

Table 1. Demographic characteristics and data in patient's histories of groups A and B.

	Number of points in group A	Number of points in group B	p between A and B
Swelling of the calf	2.4 ± 1.3	2.5 ± 1.0	0.6751
Heaviness of the legs	3.2 ± 1.1	2.8 ± 1.1	0.1038
Tiredness of the legs	3.0 ± 1.1	3.1 ± 1.0	0.8639
Heat in the legs	1.2 ± 1.3	1.2 ± 1.3	0.9366
Night muscle cramps of the legs	1.4 ± 1.3	1.0 ± 0.9	0.0821
Pain of the legs	1.6 ± 1.2	1.6 ± 1.3	0.9168
Total number of points	12.7 ± 4.4	12.1 ± 3.9	0.4495

Table 2. Patients' self-assessment during visit V1 on the basis of patient's self-assessment questionnaire (D0).

Total score	Difference in points in group A	Difference in points in group B	p between A and B
D28 – D0	-7.6 ± 3.7	-6.9 ± 3.0	0.3157
D21 – D0	-6.2 ± 3.6	-6.4 ± 2.9	0.8116
D14 – D0	-4.8 ± 3.7	-4.4 ± 3.2	0.5253
D7 – D0	-2.6 ± 2.9	-2.1 ± 2.9	0.2881

Table 3. Comparison of the self–assessment of ailments in both groups: total score comparison.

RESULTS

126 patients met the randomizing criteria, however only 119 patients underwent an assessment of partial or total therapy effectiveness as in 7 cases protocol deviations took place.

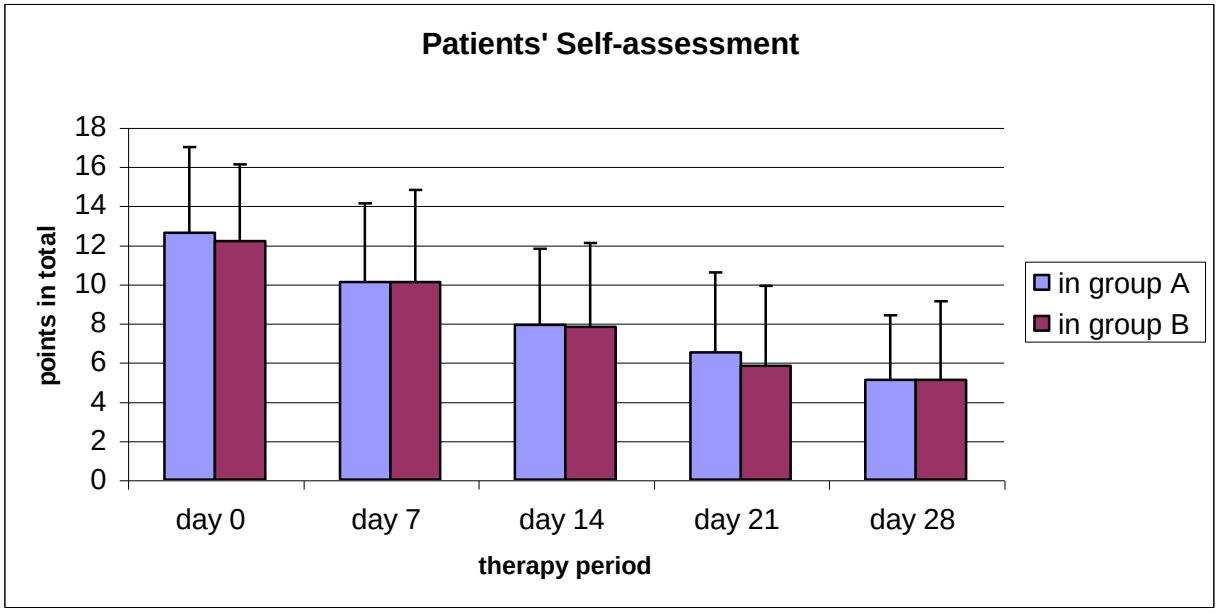

Figure 2. Average point score according to patients' self-assessment in groups A and B.

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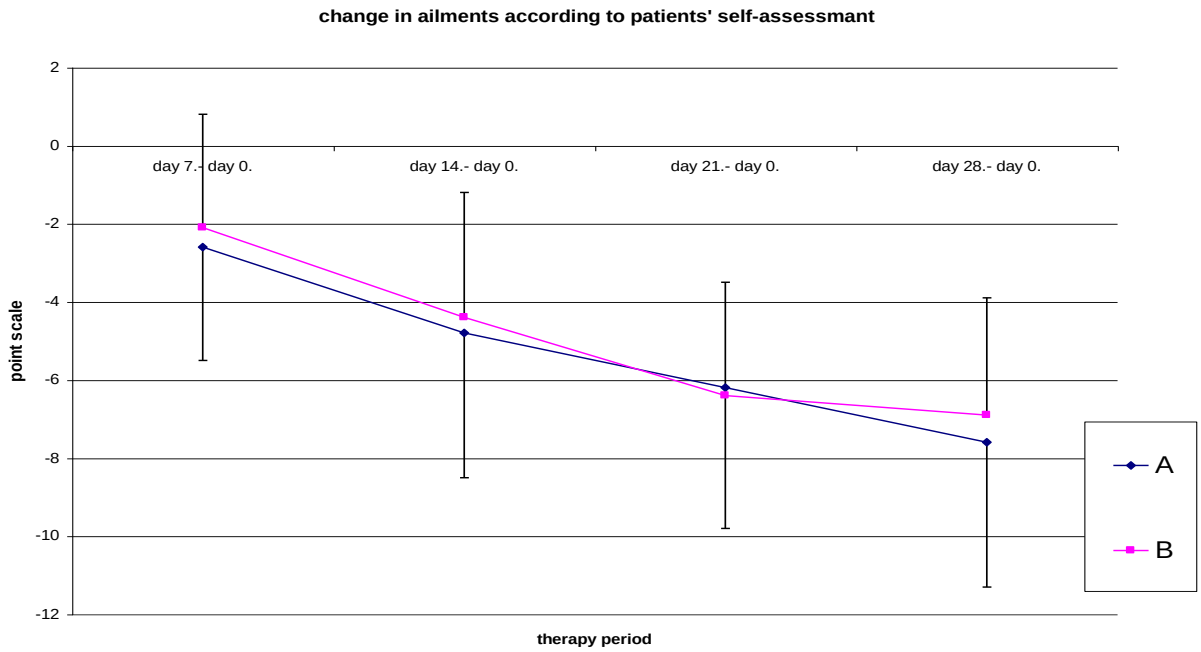

Figure 3. Decrease of ailments as a result of treatment in groups A and B in patients' self-assessment. Reduction of score in comparison to a base level, which is estimated as level 0.

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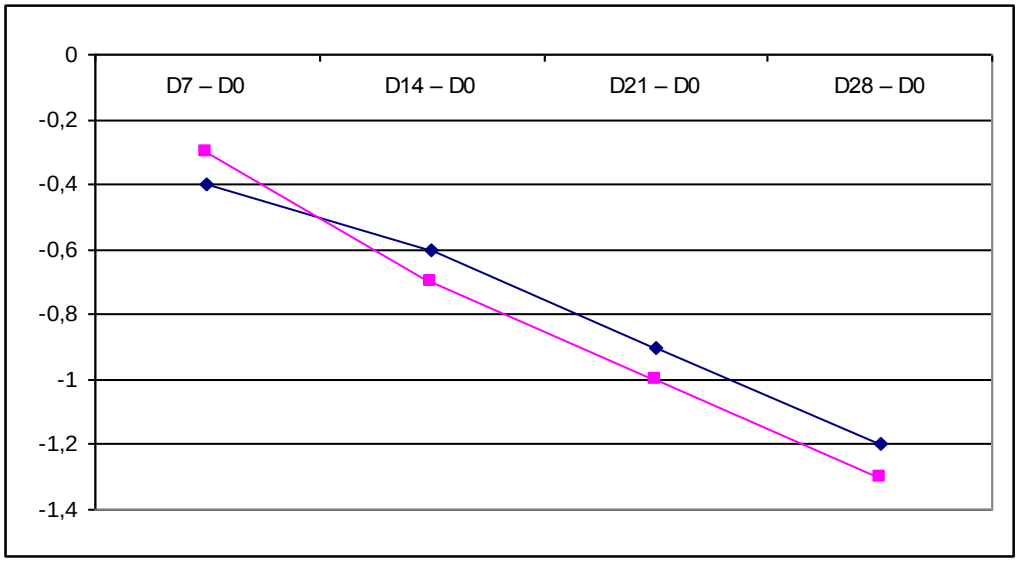
Swelling of the calf

A

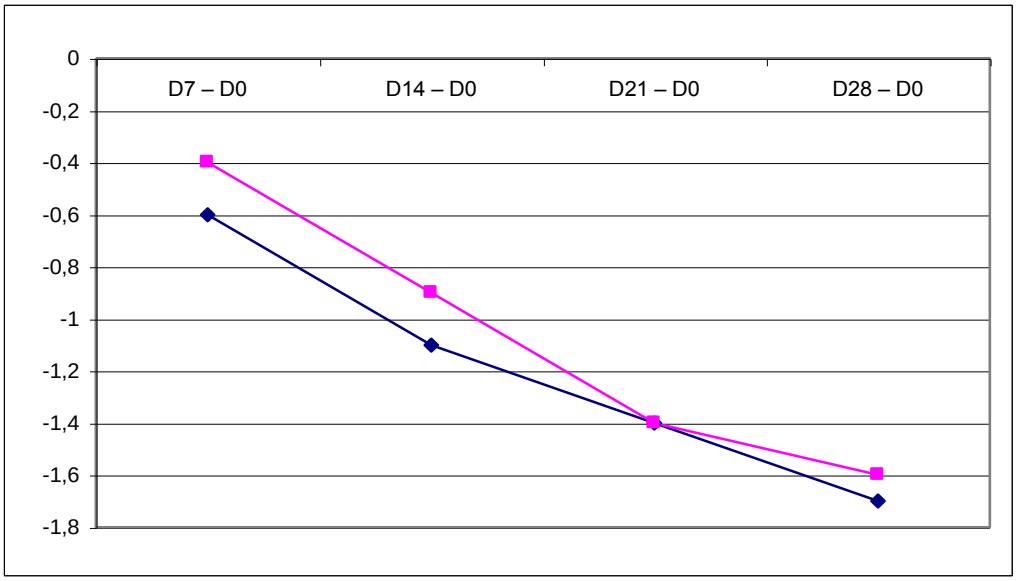
B



Heaviness of the legs

A

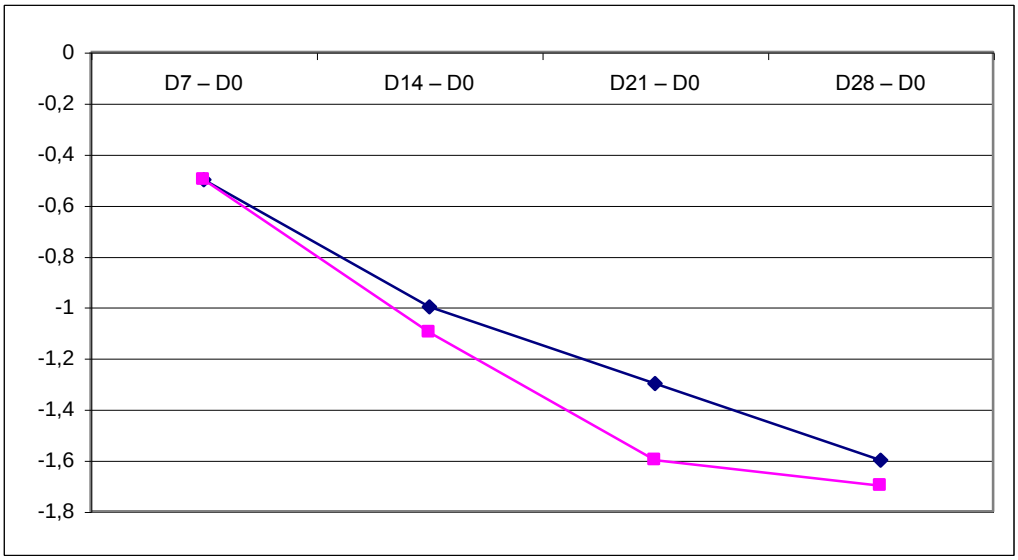
B



Tiredness of the legs

A

B



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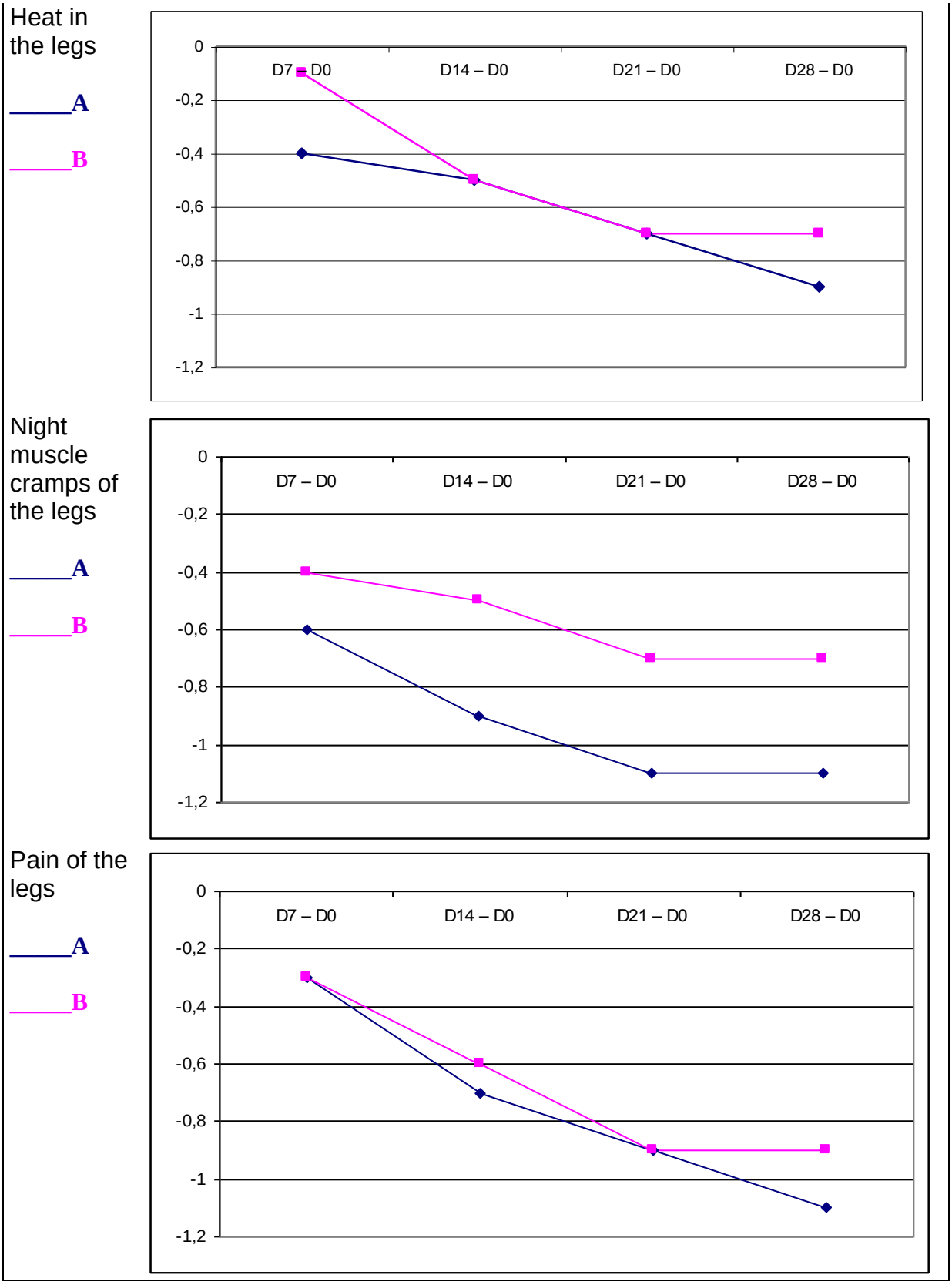

Figure 4. Comparison of the therapy effectiveness in groups A and B in the patient's self-assessment: juxtaposition of the six analyzed parameters.

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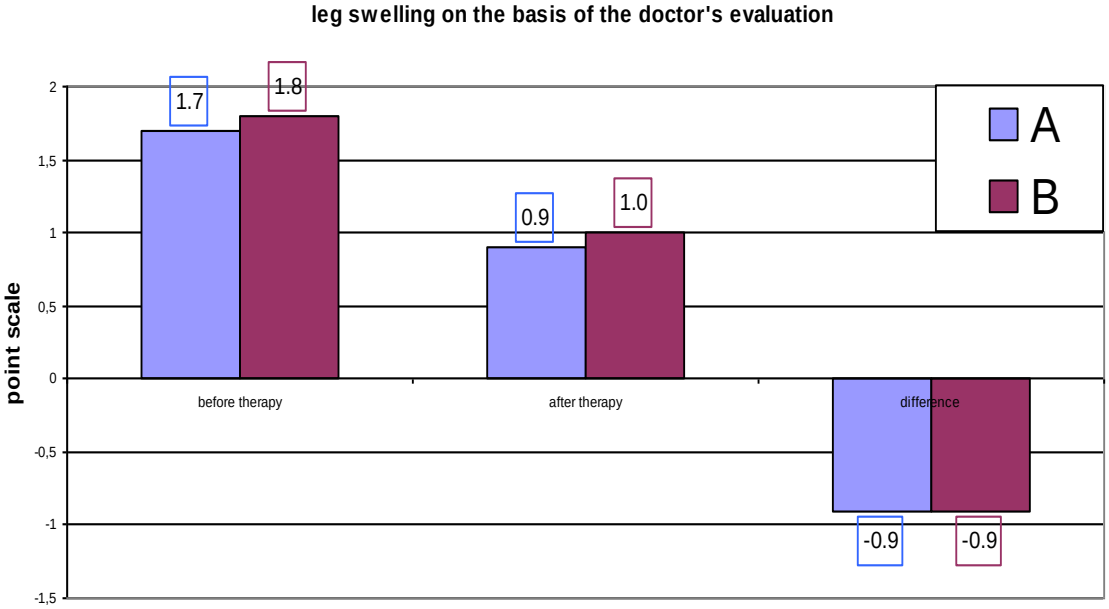
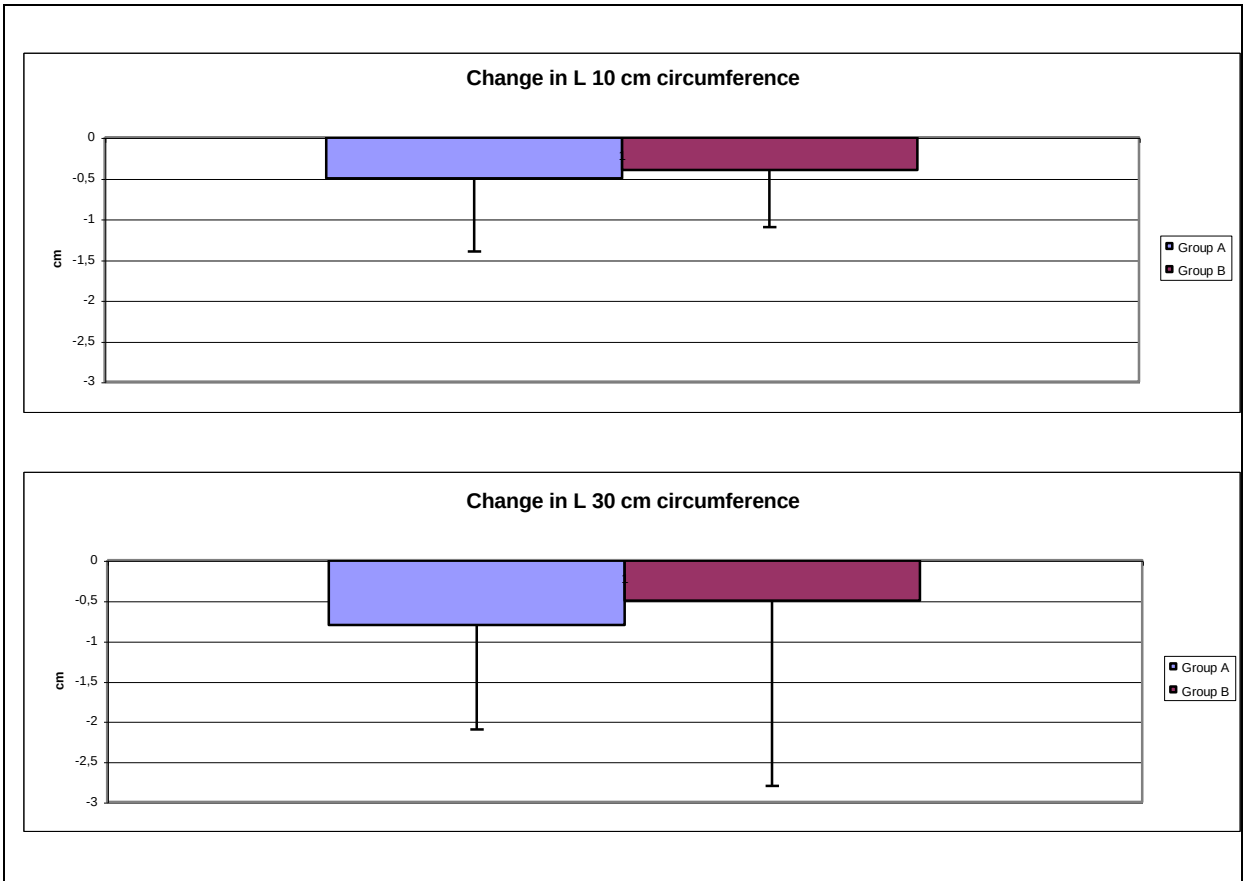


Figure 5. Change in lower limb swelling intensity in groups A and B according to the investigating physician's evaluation. Comparison between V1 and V2.

Changes in calf circumference have also been displayed in Figure 6.



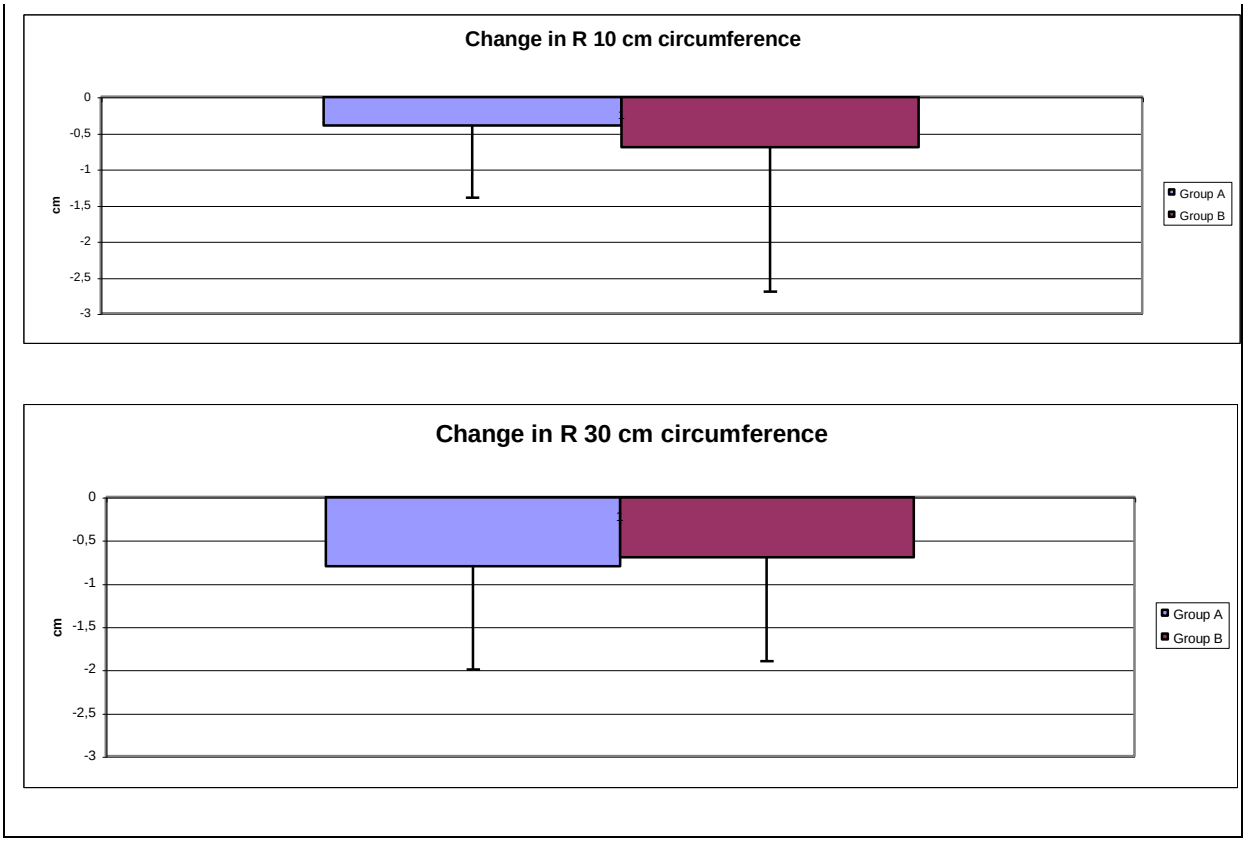


Figure 6. Comparison of calf circumference change in both groups.

Groups A and B were homogenous with respect to the demographic, interview and physical examination features studied (Table 1). No significant deviations from normal values have been recorded on blood pressure and radial and dorsalis pedis artery pulse.

During the first (initial) visit (V1) in both groups a comparable increase in the intensity of lower limb ailment was noticed, which in the total score attains on average 12.7 points for group A and 12.1 points for group B (Table 2).

The analysis of therapy effectiveness by Patients' self-assessment has shown a remarkable decrease in ailment intensity in both groups examined (Figure 2). A significant improvement had already been noticed after the first week of treatment and there was a systematic decrease in ailment intensity after each subsequent week of the therapy (Table 3, Figure 3). These differences, in comparison to the initial values on day D0 (V1), were statistically significant in both groups in all the analyses

performed (D7-D0, D14-D0, D21-D0, D28-D0) and there was no statistically significant difference in the total scores between the groups (Table 3).

The detailed analysis of ailment intensity revealed that both drugs tested acted similarly, however a tendency to more intensively reduce night cramps in the group treated with drug A has been noticed (p=0.022 on day 14, p=0.096 on day 21, p=0.074 on day 28) (Figure 4).

A comparison of average point values of swelling intensity and the skin coloration changes carried out by the investigating physician during visits V1 and V2 revealed a statistically significant reduction in swelling intensity and improvement in lower limb skin coloration in both groups, A and B (Figure 5). After a four-week therapy, the intensity of swelling decreased in group A from 1.7 to 0.9 points, and in group B from 1.8 to 1.0 points, according to the scale applied. No statistically significant differences between the groups were recorded. Unfavorable lower limb skin coloration decreased in group A from 0.8 to 0.5 points, and in group B from 0.9 to 0.5 points, respectively, according to the scale applied. Once again, no statistically significant differences between the groups were recorded.

The results of calf circumference measurements performed during visits V1 and V2 have revealed a statistically significant reduction of the calf circumference at both levels of measurements in group A, whereas in group B the difference in circumference measured at the 30 cm level proved to be insignificant (Figure 6). No statistically significant differences between the groups were recorded.

Point evaluation of the general effectiveness of the therapy conducted by the investigating physician was similar in both groups examined (2.8 points, on average, in group A and 2.5 points in group B, according to a 5 points scale). In the course of the study, the on-going observation of drug tolerance was performed. In the analysis there were reports of six adverse events, which occurred in 4 patients. None of the events was classified as serious; all adverse events led to a full recovery. As adverse effects, and thus undesirable events potentially associated with the drug administration, investigating physicians qualified two reactions in group A (calf, hands

and feet edema and body rash) and three reactions in group B (calf edema, body rash and dryness of the mouth).

Six patients were withdrawn from the study prematurely, before the term predicted by the protocol of the study (three patients interrupted the study at their own request, after the occurrence of mild adverse events). It constituted 5% of the total number of randomized patients.

DISCUSSION

The analysis of the demographic data and the initial characteristics of groups A and B have shown that examined groups were homogenous as regards all the analyzed features. It was particularly significant in the case of factors commonly considered as supportive to the development of venous insufficiency, such as: patients' age (average 45 years), inherited susceptibility to disease in their family history (in group A - 65% patients, in group B – 73 %) [8,9,12].

In both groups, a similar percentage of patients with venous abnormalities prior to the therapy was recorded (in group A – 82%, in group B - 85%). In both groups, the occurrence of additional diseases was comparable (in group A – 48%, in group B – 56 %) as well as the number of smokers (in group A - 27% patients, in group B – 31 %). Patients in both groups had had a similar level of education. In group A, 90% of patients had higher or secondary education, whereas in group B – 85% (Table 1). The high and comparable percentage of educated individuals in both groups was of importance for the quality of co-operation concerning the self-assessment questionnaire.

Due to the lack of specific and sensitive research techniques, objective assessment of the efficacy of phlebotropic drugs undoubtedly remains a problem [1,7].

Preceding studies have shown that the accepted, though unquestionably subjective method of treatment efficacy assessment is a visual scale of improvement/deterioration [3,10,11].

The self-assessment parameters presented in Tables 2 – 3 and in Figures 2 - 3 indicate that the decrease of ailment intensity with regard to venous insufficiency in both evaluated groups was of statistical significance. This concerned both the summarized total score evaluation and the single symptom point score for each of the six analyzed symptoms (Figure 4). A decrease of ailment intensity concerning all possible symptoms has already been noticed after the seventh day of treatment and systematic improvement could be observed after each subsequent week of the treatment. These differences in relation to the initial values on day D0 (V1) were statistically significant in both groups in all of the performed analyses (D7-D0, D14-D0, D21-D0, D28-D0) and for each of the 6 symptoms. Both drugs acted similarly.

Assessment of swelling and the skin coloration of the limbs carried out by the investigating physician during visits V1 and V2 showed statistically significant improvement of these parameters (Figure 5). After four weeks of treatment, the swelling intensity decreased by an average 0.9 points in both groups. No significant differences between the groups were recorded.

The use of limb circumference measurements as an indicator of a standstill in lower limb circulation meets with some difficulties, which refer to the standardization of the measurements technique as well as to a small specificity and sensitivity of the method; that is why this parameter has been estimated to be a secondary variable. Results of both calf circumference measurements before the treatment (V1) and on the last day of treatment (V2), presented in Figure 6, revealed a statistically significant decrease in lower limb circumference, measured at both levels in group A, whereas in group B the difference in measurements taken at the level of 30 cm appeared to be statistically insignificant.

The total score evaluation of the general effectiveness of the therapy (in the range of 0 to 5 points) which was carried out by the investigating physician, confirmed the similarity of both drugs effectiveness (2.8 points in group A and 2.5 points in group B).

The study is an attempt at a direct comparison of semi-synthetic diosmin, in a dose of 600 mg per 24 hours with a widely used and well clinically tested form of a drug containing a purified, micronized, flavonoid fraction of diosmin with hesperidin [1]. The results we obtained confirm the usefulness of both drugs tested, in a symptomatic treatment of patients with venous insufficiency. The study has been carried out with the use of research methods recognized in this discipline. However, a four-week observation period with reference to a chronic disease leans to further, long term studies on more extensive clinical material.

Undoubtedly a period of maintenance of the beneficial effects after the cessation of a treatment is of interest. Another problem is the effect of diosmin in men with chronic venous insufficiency, as only women participated in the above described study.

Along with the beneficial effect on chronic venous insufficiency, diosmin proved to be a safe drug. The results of the safety analysis revealed the good tolerance and safety of the administered drugs. Recorded adverse effects were mild and not numerous. The efficacy and good tolerance of both drugs refers to their strong acceptance, as about 95% of the randomized patients finished the study as specified and did not declare any reservations as to the performed treatment.

CONCLUSIONS

During the four-week observation semi-synthetic diosmin proved to reduce ailments related to lower limb venous insufficiency in women and its positive influence on symptom intensity was similar to the micronized, purified flavonoid fraction of diosmin with hesperidin.

The influence of both drugs on reducing the clinical symptoms of chronic venous insufficiency was noticeable already after one week of treatment.

Both drugs were safe and well-tolerated.