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MULTICENTER OBSERVATIONAL STUDY OF THE USE OF PHLEBODIA 600 IN PATIENTS WITH CHRONIC VENOUS DISEASE CLASSIFIED AS CEAP C0-C3

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The goal of the study was to evaluate the efficacy of diosmin (Phlebodia 600, Innothera, France) in patients with chronic venous diseases (CVD) CEAP classes C0,S-C3.

A prospective observational study to evaluate the results of two-month therapy with Phebodia 600 (600 mg of diosmine) in patients with CVD classified as CEAP C0,S-C3 was conducted. 868 patients (including 693 [79.8%] females and 175 [20.2%] males) were enrolled into the study, and 866 patients of them completed the study per protocol.

851 out of 868 patients (98.0%) followed all physician's recommendations without violations of the regimen and dosing of diosmin. The most common diosmin therapy regimen was 1 tablet taken once daily (851/868 [98.04%]). Satisfaction with diosmin therapy was assessed as "excellent" by 46.7% (CI 43.3-50.0) of patients and 49.4% (CI 46.1-52.7) of physicians, and as "good" - by 45.0% (CI 41.7-48.4) of patients and 43.6% (CI 40.3-47.0) of physicians. The quality of life score assessed using the CIVIQ-20 scale at Visit 1 was 45.4±15.4 points (median - 43.0 points). This quality of life score improved by the second visit reaching the level of 35.6±11.5 points (median - 33.0 points). By the third visit, positive changes in the parameter score over time were also observed, with the average score being 28.9±8.7 points (median - 26.0 points). At Visit 2, decrease in the left and right calf circumference (by 0.39±0.74 and 0.36±0.75 cm) was observed. The differences in the ankle circumference ("malleolar volume") measured at Visits 1 and 3 were —7.2±9.4 mm and —6.6±9.7 mm for the right and the left calf, respectively ($p<0.001$). The number of patients reporting heaviness in the legs decreased from 97.6% at the moment of enrollment to 73.0% after 2 months of therapy (which was statistically significant); the same was true for pain - from 84.5% to 55.3%, leg swelling - from 83.9% to 56.8%, cramps - from 71.2% to 35.7%, and tingling - from 63.4% to 34.1%.

Therefore, statistically significant improvement of the patients' condition was observed as early as 30 days after treatment initiation. By Day 60, the positive effect of the treatment continued to increase. The drug was found to be safe and well-tolerated, which is confirmed by low frequency of adverse events and high adherence to treatment.

Key words: *chronic venous disease, venotonic agent, diosmin, observational study.*

INTRODUCTION

Lower extremity chronic venous disease (CVD) is common among people of different sex, age and occupations. According to the results of epidemiological studies, lower extremity CVD can be found in 40% of the population [1-4]. According to other authors, CVD affects 74% of women and 56% of men [5]. In Edinburgh epidemiological study, varicose vein disease was revealed in 36.8% of cases, and chronic venous insufficiency (classified as CEAP C3-C6) - in 5.7% of cases [6]. According to the results of the International Epidemiological Program 'VEIN CONSULT', 56.39% of people in Russia have telangiectasia or reticular veins; 57.36% - varicose veins and 47.21% - leg swelling [7]. CVD results in decreased quality of life due to pain syndrome, restriction of social and daily activities, sleep disorders and temporary loss of work ability.

Several decades ago, a surgical method of CVD treatment was considered to be the only one. Over the past years, in addition to decrease in the degree of surgical procedures' trauma, the spectrum of drugs that are considered now the basis of complex therapy for CVD has increased.

The results of the Russian part of the International Research Program 'VEIN ACT' showed high popularity of venotropic medicinal products both with physicians and patients determining high patients' adherence to them [8].

Venoprotective (venotonic) agents play a major role in drug therapy for CVD. These drugs normalize the structure and function of the venous wall. The use of venoprotective agents leads to increase in venous tone, decrease in vascular permeability, improvement of lymph flow and correction of endothelial dysfunction. Moreover, these drugs may have their own anti-inflammatory effects.

According to the Russian clinical guidelines for the diagnosis and treatment of chronic venous diseases, the indications for drug therapy include: subjective symptoms of CVD; chronic venous insufficiency (C3 to C6 classes), manifestations of pelvic venous congestion syndrome, prevention of hypostasis-related or premenstrual edema, prevention and treatment of adverse events associated with surgical procedures on the lower extremity veins [9]. 2017 Clinical guidelines for the management of varicose veins not accompanied by chronic venous insufficiency recommend to use oral venotropic agents as safe drugs for elimination of CVD symptoms if such symptoms are present [10]. According to the Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum [11], the venoactive agents may be used for reduction of swelling and relief of pain associated with CVD (recommendation grade II, evidence level B); the same role of venotropic therapy is stated in the Clinical practice guidelines of the European Society for Vascular Surgery (ESVS) regarding CVD treatment [12] (recommendation grade IIa, evidence level A).

Phlebodia 600 (a drug containing diosmin 600 mg) is a venotonic agent with a comprehensive mechanism of action that involves key steps of CVD pathogenesis. Phlebodia 600 has a phlebotonic effect - it reduces venous distensibility, increases the venous tone (dose-dependent effect), reduces venous stasis, improves lymphatic drainage and microcirculation (by increasing the capillary resistance), reduces capillary permeability, reduces adhesion of leukocytes to the venous wall and their migration into the paravenous tissues, and it also produces an anti-inflammatory effect. The results of studies conducted earlier [13-16] demonstrated that the drug is effective at the dose of 600 mg taken once daily for 1 to 3 months.

This study was initiated with the purpose to obtain and evaluate the results of use of the drug in real clinical practice, to assess patient and doctor satisfaction with the results of the drug use, to assess the compliance with the protocol criteria, the effects of its use on CVD symptoms and the quality of life of patients with CVD.

The primary goal of the study was to evaluate the patient and doctor satisfaction with Phlebodia 600 treatment in routine clinical practice.

The secondary goals include the following:

- to describe the patient group (demography, condition, concomitant and prior therapy);
- to assess the quality of life of patients (CIVIQ-20 questionnaire);

- to evaluate the tolerability of the drug;
- to describe and evaluate the symptoms of CVD and their severity;
- to evaluate Phlebodia 600 therapy regimens;
- to evaluate the compliance with the protocol criteria (including the reasons for treatment discontinuation);
- to describe adverse events associated with Phlebodia 600 administration.

MATERIALS AND METHODS

Study design The multicenter prospective observational study was conducted from May 2016 to February 2017 in 86[*] (this footnote is located at the end of the article and contains the list of physicians who participated in the study) study sites in 22 cities of the Russian Federation. The patients were followed up according to the routine practice of the healthcare facilities. The patients received diosmin (Phlebodia 600) according to the patient information leaflet. Three visits were conducted during the study - one visit for the patient inclusion and two follow-up visits, which were conducted in accordance with routine clinical management of such patients roughly once a month.

Study population. The patients prescribed to take Phlebodia 600 for the treatment of CVD as a part of routine clinical practice were offered to participate in the study. Taking into account the non-invasive nature of the study, the decision regarding the therapy prescription was independent of the patient's inclusion into the study.

Inclusion criteria:

1) male and female patients aged 25-75 years with CVD classified as CEAP C0,S-C3, who were prescribed Phlebodia 600;
2) signed and dated Informed Consent Form to participate in the study.

Non-inclusion criteria:

1) contraindications for the use of Phlebodia 600;
2) pregnancy;
3) any medical or non-medical reasons that, in the physician's opinion, may impede the patient participation in the study.

A total of 868 patients were enrolled into the study, including 693 (79.8%) females and 175 (20.2%) males aged from 25 to 75 years. The number of female patients was four times higher than the number of male patients ($p<0.001$). The average age of female and male patients was 45.7±13.3 years and 43.1±13.5 years, respectively. Female study subjects were older than males subjects ($p=0.024$). The characteristics of enrolled patients are shown in Table 1.

[*] *86 clinical research physicians, 8 supervising physicians:*

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Table 1

Characteristics of patients enrolled into the study

Parameter	Abs. number (N=868)	%
Duration of chronic venous disease		
Less than 1 month prior to enrollment into the study	502	57.8
1 to 678 months (Me=45.9 months; interquartile range 25-75% [8.4-122.7] months)	366	42.2
CEAP stage		
C0,S	7	0.8
C1	208	24.0
C2	377	43.4
C3	276	31.8
Prior therapy		
Drug therapy	390	44.9
Surgical procedures	221	25.5
Compression therapy	456	52.5

Table 2

Prior drug therapy

Therapy variant	Abs. number (N=868)	%
Diosmin + Hesperidin	158	40.5
Diosmin	142	36.4
Troxerutin	116	29.7
Aescin	5	1.3
Gingko biloba	4	1.0
Other	14	3.6

Table 3

Variants of surgical treatment (n=221)

Type of surgical treatment	Abs. number	%
Sclerotherapy	66	29.9
Endovascular procedures (thermal ablation)	54	24.4
Open surgery on lower extremity veins	121	54.8
Other	2	0.9

The most common types of prior therapy for CVD were diosmin taken both as a monotherapy and in combination with hesperidin 142/390 (36.4%) and 158/390 (40.5%), respectively. Table 2 presents the data on drug therapy that the patients received prior to the most recent prescription of diosmin.

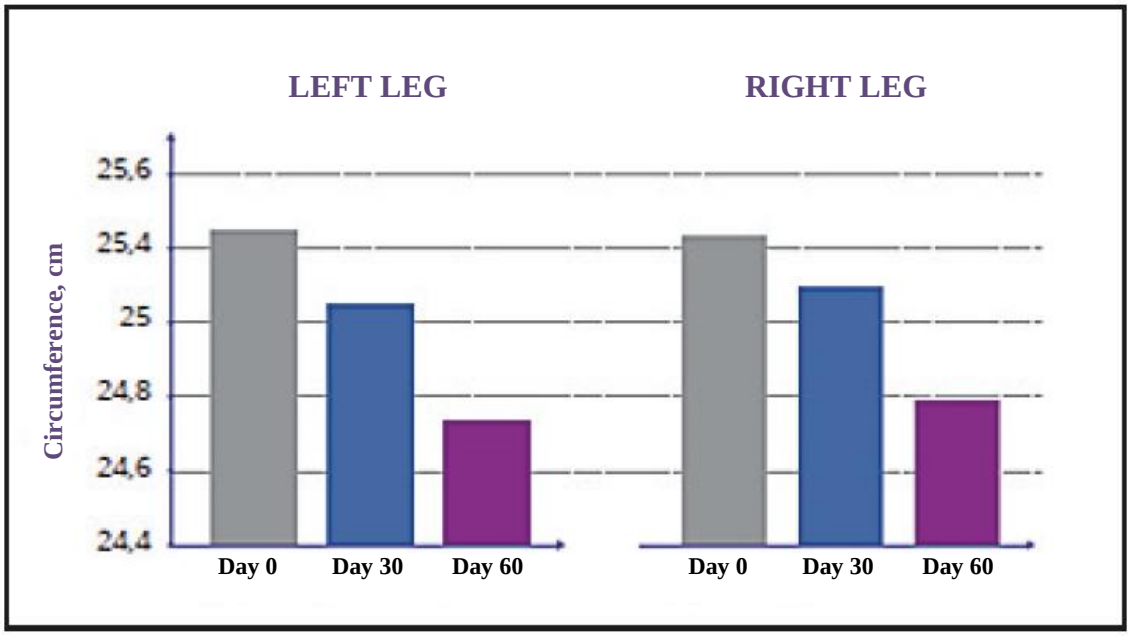

Fig. 1. Changes in the calf circumference over time (malleolar volume)

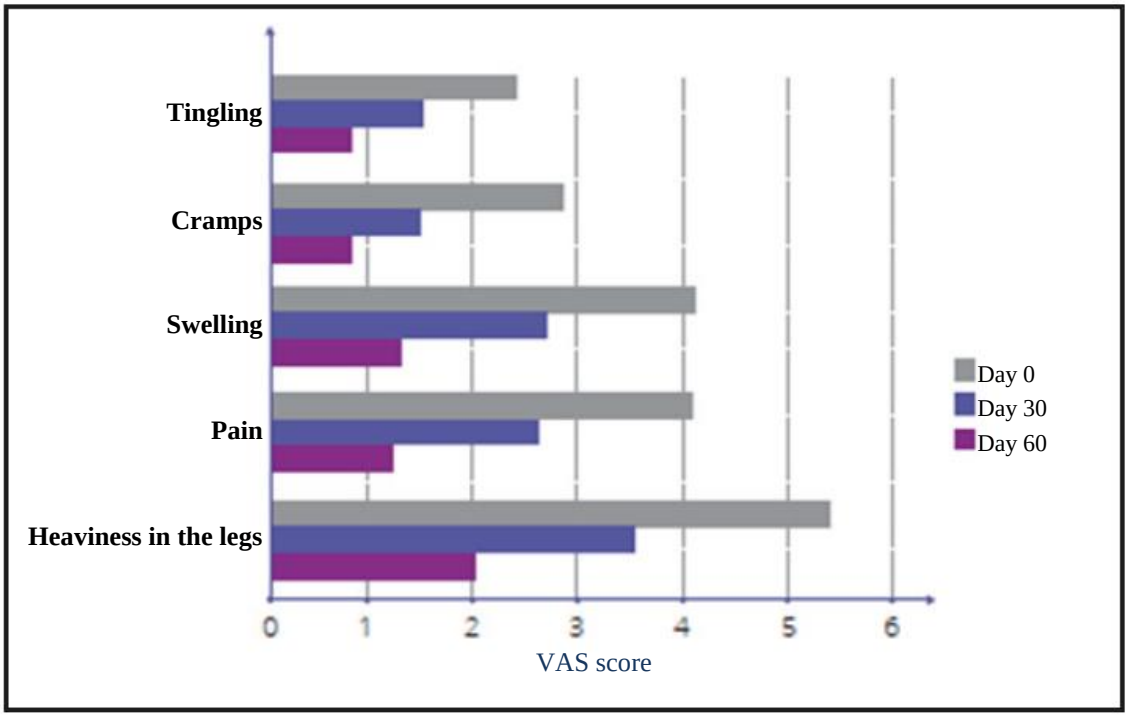

Fig. 2. Changes in severity of symptoms of chronic venous disease over time

Surgical procedures mainly included open surgery on the lower extremity veins - 121/221 (54.8%), which is shown in Table 3. Class 2 (23-32 mm Hg) and class 1 (15-21 mm Hg) compression stockings were used in 290/456 (63.6%) and 136/456 (29.8%) cases, respectively. Compression therapy for more than 4 weeks was registered in 323/456 (70.8%) patients.

Statistical methods. Statistical analysis was conducted using the standard IBM SPSS Statistics software package, version 22.0.0. Two-sided critical p-values and confidence intervals were calculated. The level of statistical significance was accepted at 0.05. To describe continuous variables, the arithmetic mean, standard deviation, 95% confidence intervals (CIs), median, upper

and lower quartiles were used. Categorical variables were presented in the form of percentages and 95% CI. To test the significance of differences between normally distributed data, the respective variants of Student's t-test were used. For other distributions, the Wilcoxon test was applied. To test the significance of differences between the categorical data, a chi-squared test or Fisher's exact test were used. Per protocol population included all patients who had come to all three scheduled visits.

RESULTS

851 out of 868 patients (98.0%) followed all physician's recommendations without violations of the regimen and dosing of diosmin. The remaining 17 patients missed some of their doses (221 tablets in total). Two patients discontinued the drug at their own will (total number of missed days (tablets) was 37). Intolerance was not the reason for treatment discontinuation in any of the cases.

The most common diosmin therapy regimen was 1 tablet taken once daily (851/868 [98.04%]). Only in 17/868 (1.96%) cases the drug was prescribed as follows: 1 tablet twice daily. No other therapy regimens were registered.

The study demonstrated high level of satisfaction of both physicians and patients with the drug. There were no statistically significant differences between the assessment of Phlebodia 600 by patients and physicians (Table 4).

Table 4.

Satisfaction with treatment assessed by physicians and patients (n=866)

Assessment	Patients		Physicians		p
	Number	95% CI	Number	95% CI	
Excellent	404 (46.7%)	43.3-50.0	428 (49.4%)	46.1-52.7	0.261
Good	390 (45.0%)	41.7-48.4	378 (43.6%)	40.3-47.0	0.587
Satisfactory	64 (7.39%)	5.74-9.34	53 (6.12%)	4.62-7.93	0.293
Bad	7 (0.81%)	0.33-1.66	7 (0.81%)	0.33-1.66	1.000
Very bad	1 (0.12%)	0.00-0.64	0 (0.00%)	0.00-0.43	0.308

To assess the results of treatment, the changes over time in the quality of life were studied using CIVIQ-20 questionnaire (20 points - the best result; 100 points - the worst result). The quality of life score assessed using the CIVIQ-20 scale at Visit 1 was 45.4±15.4 points (median - 43.0 points). This parameter improved by the second visit reaching the level of 35.6±11.5 points (median - 33.0 points). By the third visit, positive changes in the parameters over time continued to be observed, with the average score being 28.9±8.7 points (median - 26.0 points).

Evaluation of statistical significance of the changes in the parameters assessed using the CIVIQ-20 questionnaire demonstrated that the parameter decreased by the second visit reaching the level of 9.85±8.03 points ($p<0.001$). By the third visit, this parameter decreased by 16.6±11.5 points as compared to baseline ($p<0.001$).

For objective assessment of the swelling degree, the malleolar volume - the circumference at the level of the narrowest part of the calf above the ankles - was measured in cm. Serial measurements of the malleolar volume on both legs showed its statistically significant decrease as early as by Visit 2 as well as by the end of the study ($p<0.001$). The decrease in the left and right calf circumference (by 0.39±0.74 and 0.36±0.75 cm, respectively) was observed at Visit 2. The rate of swelling regression was substantially lower afterwards. Despite that, the differences in the ankle circumference ("malleolar volume") measured at Visits 1 and 3 were 7.2±9.4 mm and 6.6±9.7 mm for the left and the right calf, respectively ($p<0.001$). There were no significant differences between the changes observed in the left and the right calf. The results are shown in Fig. 1.

Statistically significant positive changes over time were observed in respect of the frequency and severity of all CVD symptoms evaluated using the Visual Analogue Scale (VAS) from 0 (no

symptom) to 10 (maximum severity of the symptom). During each visit, the presence and severity of such symptoms as heaviness, pain, swelling, cramps and tingling in the lower extremities were assessed. While on therapy with diosmin, the patients demonstrated positive changes over time by Visit 2; even more marked results were recorded at the end of the study (Visit 3). Thus, the frequency of heaviness in the legs showed statistically significant decrease from 97.6% at the moment of enrolment into the study to 73.0% after 2 months of treatment. The frequency of pain decreased from 84.5% to 55.3% cases, complaints of leg swelling - from 83.9% to 56.8%, complaints of cramps from 71.2% to 35.7%, and tingling from 63.4% to 34.1% (Fig. 2).

The total number of adverse events, which were registered in 5 (0.58%) patients receiving the drug was 6. The causal relationship between the AE and the drug was considered certain in one case (nausea), probable in 2 cases (non-intense stomach pain and dyspepsia), unlikely - in one case (headache), and lack of relationship was found in two cases.

One adverse event was considered serious because of the need of hospital admission - acute thrombosis of the left popliteal vein in a 52-year-old female patient with known thrombophilia. Following anticoagulant and compression therapy, recanalization of the thrombus was observed without signs of pulmonary thromboembolism. Therapy with diosmin was not interrupted. This event was considered unrelated to the studied therapy.

DISCUSSION

The peculiar feature of this study is involvement of CEAP clinical classes of CVD that the patients most commonly have when they present to a specialist.

In an open-label observational population study by Zuccarelli F. [13], which was published in 1990 and enrolled 16,728 patients with lower extremities edema caused by venous insufficiency, three-month therapy with Phlebodia 600 resulted in edema reduction (decreased ankle circumference) and elimination of CVD symptoms (in 92% cases). The satisfaction of patients with the treatment was 92%. In the specified study, only the results of treatment of patients with edema caused by either functional or structural pathology were analyzed. It should also be noted that 76% of female patients enrolled in the study were pregnant. The results of our study are similar to those obtained in a multicenter randomized comparative clinical study by Cazaubon M., et al. [15], which based on the experience of treatment of 1422 patients with C0,S-C3 class CVD with diosmin in different pharmaceutical forms.

Undoubtedly, lots of large clinical studies of efficacy and safety of venotropic therapy for CVD have been conducted since then. A number of comparative studies have demonstrated the efficacy and safety of diosmin used for CVD treatment. A multicenter double-blind randomized comparative clinical study by Henriet J.P. [16] demonstrated similar efficacy of once daily intake of diosmin 600 mg and twice daily intake of a combination of flavonoids (500 mg) containing 90% of diosmin, in respect of elimination of CVD symptoms in females receiving hormonal contraceptives. Another multicenter clinical study by Maruszynski M., et al. [14] evaluated the influence of diosmin and micronized purified flavonoid fraction (diosmin and hesperidin) on symptoms of chronic venous insufficiency in 126 patients. The analysis of treatment efficacy based on patient self-assessment showed substantial reduction in the symptoms' severity in both groups studied. The decrease in severity of manifestations of venous insufficiency in both groups was statistically significant.

In our study, we have obtained new data regarding the efficacy and safety of diosmin used for treatment of patients with CVD of C0,S-C3 CEAP classes. This study is the largest epidemiological clinical study that has been conducted so far.

The results of prospective observational study have proven the efficacy of diosmin 600 mg once daily in patients with CVD of C0,S-C3 CEAP classes. After two months of observation, statistically significant decrease in the parameters assessed using CIVIQ-20 questionnaire was achieved, along with statistically significant reduction in the calf circumference, and the severity of CVD symptoms. More than 90% of patients and physicians assessed the obtained result as

"good" or "excellent". In the study, the drug was found to be well-tolerated and associated with good adherence to treatment.

CONCLUSIONS

1. The result of two-month treatment with diosmin (Phlebodia 600) in patients with CVD (CEAP C0,S-C3 classes) is assessed by patients and physicians as "good" or "excellent" in 90% of cases.

2. Diosmin use as a monotherapy or as a part of combination therapy for CVD (CEAP C0,S-C3 classes) results in improvement of the patients' quality of life, elimination of venospecific symptoms or decrease in their severity, swelling reduction.

3. The therapy regimen for diosmin (600 mg once daily) was followed in 98.0% cases suggesting high level of adherence to this treatment modality.

4. High safety profile of Phlebodia 600 has been confirmed in this study.

No conflicts of interest.

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