



Medicamentous treatment of chronic venous insufficiency using semisynthetic diosmin – a prospective study

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Introduction: Chronic venous insufficiency (HVI) is manifested by the progressive signs of venous stasis. This disorder is treated by: compressive bandaging, medicaments, sclerotherapy, surgery, etc. **Aim:** Prospective study of the effects of semisynthetic diosmin (clinical signs, quality of life, local biochemical parameters) on patients with HVI to whom no other method of treatment has previously been administered. **Method applied:** This prospective study analysed the presence of risk factors and personal history of 80 patients with HVI. Diagnosis of HVI was based on the clinical appearance and the color duplex scan. Each patient's clinical signs (pain, oedema, feeling of heaviness and tightness in the lower leg), quality of life (physical, social, and psychological), and CEAP stage were assessed prior to and 30 days after the treatment with Phlebodia 600[®]. For 15 patients with unilateral varicose veins, local values of lactates and gas analysis were taken under the conditions before and following the static load, and venous control samples were taken from the healthy leg. The acquired data were processed by means of descriptive statistics, while the significance of nonparametric features was measured by Wilcoxon test. **Results:** HVI is somewhat more frequent among females than among males, on the left than on the right leg, and at the average age of 52.3 ± 10.5 . The patients with HVI are basically engaged in professions with static load and have positive family history. The patients mainly started medical treatment 12.5 ± 8.6 years after the first symptoms of the disease. Clinical improvement was recorded on the state of 65/80 patients. After the treatment numerical values of some of the clinical signs were statistically lower compared to the values before the administration of semisynthetic diosmin: oedema (0.94:1.50), pain (1.10:1.84), feeling of heaviness (1.20:1.96), and tightness (1.14:1.78). After the administration of the tested medication, parameters of physical, social, and psychological quality of life were significantly improved

($p < 0.0001$), accompanied with significantly improved ($p < 0.0001$) CEAP stage of HVI (3.00:3.40). Local biochemical parameters had not been significantly changed. **Conclusion:** Administration of semisynthetic diosmin during 30 days results in significant improvement of clinical signs, quality of life and CEAP stage of HVI.

Key words: HVI, CEAP, semisynthetic diosmin, quality of life.

INTRODUCTION

Chronic venous insufficiency (HVI) represents a number of complex pathological conditions which lead to progressive venous stasis because of the constant increase of venous pressure, and consequently to inflammatory and trophic lesions of skin, subcutaneous tissue, and subfascial structures of the distal parts of lower limbs. Lipodermatosclerosis and venous ulcer are the terminal stages of HVI. It is supposed that approximately one half of entire European and North American adult population suffers from some degree of HVI.

The classification of HVI is based on clinical manifestations and other characteristics of the disorder. The earlier classification used to describe four stages of HVI: asymptomatic, mild, moderate, and severe venous stasis. However, CEAP classification has been generally adopted: C – clinical manifestations, E – etiology, A – anatomical distribution, P – pathophysiology (Table 1).

Venous ulcerations appear in approximately 1-2% of Western countries population. The prevalence of this disorder is between 2 – 6.4/1000 and is connected with the patient's age. The average age of the patient is lower for men (67, range 22-96), than for women (74, range 21 – 100). The disorder is more frequent among women than among men (ratio 3:2)². Socioeconomic significance of the disorder is enormous. In the USA approximately 2,000,000 working days are lost annually due to venous ulcers³.

Annual expense of British health care fund for treating venous ulcerations is estimated to be 100- 400 million £, i.e. each unhealed venous ulceration costs at least 1.200£ per year⁴. Moreover, the indirect costs (absence from work, permanent disability and early retirement) additionally increase the cost of the treatment of such patients. Thus, it is important to start the treatment in the early stages of CEAP, instead in the terminal stage of HVI.

HVI is a result of the incompetence of the superficial, deep, and perforating veins. 10-25% of all patients with HVI and venous ulcers are diagnosed as having isolated incompetence of the superficial veins, and 15% of patients are diagnosed as having isolated incompetence of perforating veins⁵.

The incompetence of the deep veins leads to severe local metabolic disorders and ulcerations refractory to treatment^{5,6}. Venous reflux is rarely isolated to a single segment of a vein, but rather results in a progressive stasis and disorder of complete venodynamics. Therefore, pathological reflux of blood through the incompetent perforating veins significantly increases microcirculation pressure as a rule, which was observed at all HVI patients⁶.

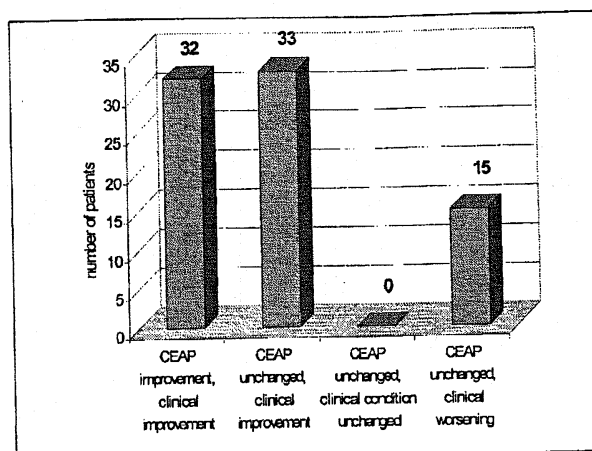
This leads to subcutaneous oedema and changes in the skin (lipodermatosclerosis), usually accompanied with eczematous dermatitis. The oedema progressively interferes with the normal transportation of the nutritious substance to the tissue because of the high interstitial pressure, which results in a capillary collapse with increased blood flow in lipodermosclerotic and ulcerated skin^{2,3}.

There are several theories dealing with venous ulcerations: stasis, and hypoxia, pathological arterial-venous fistulas, pericapillary blockade of exchange, and Le entrapment^{2,3}.

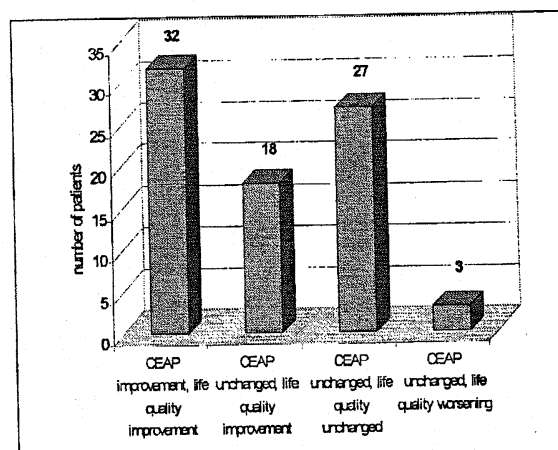
The most important symptoms and signs of HVI are swelling, pain, feeling of heaviness and tightness in the legs. Persistent and progressive nature of these symptoms leads to physical, social, and psychological suffering of patients, significantly affecting their quality of life^{2,3,5}.

The diagnosis of HVI is based on the personal history, clinical examination, color duplex scan, and rarely other diagnostic procedures (phlebography, CT, MRI)^{3,5}. Treatment for HVI should be based on etiology, pathogenesis, and CEAP classification of venous stasis. There are several agents used for treatment: local treatment, graded elastic compressive bandage, drugs, sclerotherapy and surgery.

Treatment for HVI should be started as soon as possible, i.e. before the ulcerations develop. External compressive bandage had been used for venous disorders ever since Hippocrates. It was shown that this treatment improves flow through the magistral veins as well as micro vascular dynamics by reducing oedema and improving skin nutrition². Graded compression (30 - 40 mmHg on medial malleolus) is more effective than a uniform bandage². Compression by elastic stockings or bandages reduces lipodermatosclerosis and significantly improves healing of venous ulcerations^{2,5}, thus it is indicated either independently or as adjuvant therapy for HVI and venous



GRAPH 1.
EFFECT OF SEMI SYNTHETIC DIOSMIN ON CEAP STAGE AND THE CLINICAL SIGNS



GRAPH 2.
EFFECT OF SEMI SYNTHETIC DIOSMIN ON CEAP STAGE AND QUALITY OF LIFE

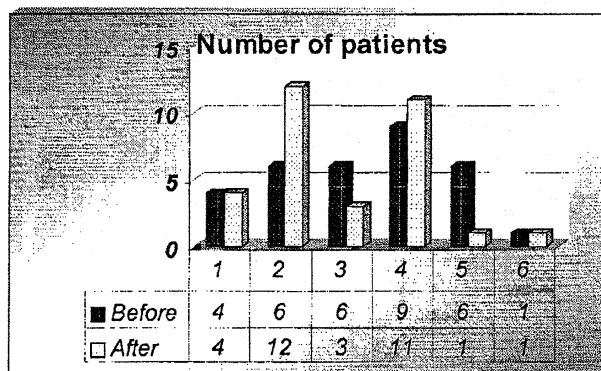
ulcerations. The administration of medicaments to HVI patients should be rational and based on the established microcirculation disorders. Hydroxy-rutosides, flavonoids from plant glycosides, reduce the rate of capillary filtration which reduces oedema and results in a clinical improvement of HVI².

Semisynthetic diosmin (7-rhamnoglucoside 5,7,5' - tri-hydroxy 4-methoxy flavone) acts selectively venotonic, vasculoprotective and anti-inflammatory⁷.

THE AIM

The aim of the study is to examine the following HVI parameters, before and after the administration of semi synthetic diosmin:

1. clinical symptoms and signs of HVI (pain, swelling, heaviness, and tightness),
2. quality of life (physical, social, psychological),
3. stage of CEAP classification,
4. local metabolic status (lactates, gas analysis).



GRAPH 3.
DISTRIBUTION OF PATIENTS BY CEAP STAGES BEFORE AND AFTER THE ADMINISTRATION OF SEMI SYNTHETIC DIOSMIN

TABLE 1

CEAP CLASSIFICATION OF CHRONIC VENOUS INSUFFICIENCY

Class	Definition
Clinical Signs (0-6): "A"-asymptomatic, "S"-symptomatic	
0	No obvious of palpable signs of chronic venous disease
1	Telangiectasias of reticular veins
2	Varicous veins
C	3 Oedema
	4 Skin disorders attributable to venous (hyperpigmentation, etc.)
	5 Previously defined skin disorders+ cured venous ulcer
	6 Previously described skin disorders +active (constant) venous ulcer
E	Etiologic classification: congenital, primary and secondary
A	Anatomic distribution: superficial, deep, perforated/ a - isolated, combined
P	Pathophysiological disorder: reflux, obstruction/ a - isolated, combined

MATERIALS AND METHODES

The prospective study (from 1st November 2007. to 31st January 2008.) included 80 ambulatory patients who agreed to receive only medicament treatment (Phlebodia 600®, Innotech International, France, single daily dose)

for their HVI during a month, without using the elastic bandage or any other agents. Each patient's risk factors, family history, personal history, clinical symptoms and Doppler test (Doppler index, CDS US flow through lower limbs veins) were taken. Patients with arterial disorders and non-venous vascular disorders (Doppler index below 0.96) were not included in the study.

Each patient's clinical signs (pain, oedma, feeling of heaviness and tightness in the lower limbs, measured on a scale from 0 to 3, 0 meaning no symptoms were found), quality of life - physical, social, and psychological parameters (a scale from 1 to 5, 5 representing the most favourable degree), and CEAP classification of HVI were assessed prior to and 30 days after the treatment with semisynthetic diosmin. 15 patients with unilateral HVI took additional tests: lactates (mmol/l) and gass analysis: acidity (pH), partial oxygene pressure pO₂ (mmol/l), oxygene saturation - SO₂ (%), partial pressure of CO₂ - pCO₂ (mmol/l), and total CO₂ - T CO₂ (mmol/l) in the venous blood samples taken from the affected region (B sample), and an approximate level of the collateral, helaty leg (Z sample) while resting (0 sample), and after 30 minutes of passive standing (S sample). All samples were taken directly before the study started (day 0) and after one - month treatment with the tested medication (day 30).

The results were processed by means of descriptive statistics (mean value - \bar{X} , and standard deviation - SD), while the statistic significance of nonparametric features was measures by Wilcoxon signed-rank test (Z).

THE RESULTS

HVI appeared to be somewhat more frequent among women (48) than among men (32), but the difference was not significant. The youngest patient was 36, and the oldest 84 years old ($\bar{X} \pm SD = 52.3 \pm 10.5$). HVI was diagnosed on the left leg (26), right leg (36) or bilaterally (18). Patients were mostly (46; 57.5%) working under static load. Women had from 0 to 3 deliveries ($\bar{X} \pm SD = 1.5 \pm 0.7$), and from 0 to 10 ($\bar{X} \pm SD = 3.5 \pm 2.6$) abortions. Positive family history was found at 51 (63.8%) patients. The patients had a personal history of the disorder from 3 to 38 years ($\bar{X} \pm SD = 12.5 \pm 8.6$). Symptoms and signs of venous stasis were more prominent before than after the treatment, and the difference was significant (Table 2).

The administration of the medicament treatment resulted in a significant improvement of the quality of life parameters (Table 3)

The treatment with Phlebodia 600® during a month resulted in an improvement of CEAP stage for 32 patients, with regression of the symptoms and improvement of quality of life. For 48 patients there was no change in CEAP status, but for 35 among them the clinical symptoms of HVI were reduced, while the deterioration of the clinical symptoms was recorded for 15 of them. Thus the clinical improvement of the symptoms was recorded for 65 of 80 patients (Graph 1). The administration of semi synthetic diosmine resulted in an improvement of CEAP stage and quality of life for 32 patients. For the 48 patients

TABLE 2

CLINICAL SYMPTOMS AND SIGNS OF HVI FOR 80 PATIENTS BEFORE AND 30 DAYS AFTER

Symptom	Scale 0-3	Before the treatment	After the treatment	Significance (Z)
Swelling	$\bar{x} \pm SD$	1,50 \pm 0.87	0,94 \pm 0.72	5,392 $p < 0,001$
Pain	$\bar{x} \pm SD$	1,84 \pm 0.74	1,10 \pm 0.89	6,368 $p < 0,001$
Heaviness	$\bar{x} \pm SD$	1,96 \pm 0.86	1,20 \pm 0.1,00	6,121 $p < 0,001$
Tightness	$\bar{x} \pm SD$	1,78 \pm 1,22	1,14 \pm 1,06	5,16 $p < 0,001$

TABLE 3

QUALITY OF LIFE OF 80 PATIENTS BEFORE AND 30 DAYS AFTER THE ADMINISTRATION OF SEMISYNTHETIC DIOSMIN

Quality of life (Scale - 5)		Before the treatment	After the treatment	Significance (Z)
Physical	$\bar{x} \pm SD$	3,73 \pm 0.87	4,11 \pm 0.80	5,090 $p < 0,001$
Social	$\bar{x} \pm SD$	3,75 \pm 0.86	4,14 \pm 0.91	5,070 $p < 0,001$
Psychological	$\bar{x} \pm SD$	3,78 \pm 1,17	4,10 \pm 1,11	4,087 $p < 0,001$

with an unchanged CEAP stage, the quality of life was assessed as improved (18), worsened (3), unchanged (27), (Graph 2).

One-month treatment with diosmin resulted in a significant improvement of redistribution of patients by CEAP classification (Table 4, Graph 3).

Although the level of lactates measured prior to treatment, and under static load, was higher comparing to the levels after the treatment, the difference was not significant (Table 5).

DISCUSSION

Chronic venous insufficiency affects women more frequently, but the difference is not as significant as it used to be described, because increasing number of men is getting affected by HVI. In our population women:men ratio was 3:2.5. The disorder affects adult population, no matter the age.

However, its incidence is the largest in the sixth and seventh decade¹⁰. Our population included somewhat younger patients (\bar{x} SD = 52.3 10.5). The professions requiring long – lasting passive static load may be considered a significant risk factor for HVI. This finding is consistent with all relevant studies^{5,11}. Similarly, HVI is more frequent among patients with a positive family history^{2,5,11}. The duration of the symptoms of the patients included in our study varied (3 to 38 years), which is also consistent with other studies⁹.

The most frequent and the most prominent clinical signs of venous stasis are feeling of heaviness and tightness, followed by pain and swelling^{2,5,11}. Being persistent and marked, these symptoms significantly interfere with physical, social, and psychological quality of life¹⁰. With the exception of feeling of tightness, which appears to be less frequent, all other symptoms were almost identical for all our patients and consistent with similar prospective studies^{2,9}.

The frequency of the symptoms and the signs of HVI were significantly improved after a month of treatment with semi synthetic diosmin (Table 2), as in similar studies. Thus, the improvement of all parameters of quality of life achieved with this agent is highly significant (Table 3), as found also by other researchers^{2,9}. A month of treatment with semi synthetic diosmin resulted in an improvement of CEAP stage of HVI for the half of the treated patients, and for the most of the patients without an improvement of CEAP a relevant clinical improvement was recorded (Table 4, Graph 1).

Results of distribution by CEAP stages and patients' quality of life with HVI were similar (Table 3, Graph 2). Pinjala et al.⁹ reported that purified flavonoid fraction administered for 6 months to 308 patients with HVI resulted in regression of CEAP stage (53.9%), did not change CEAP stage but decreased the symptoms (29.5%), did not change CEAP but resulted in a deterioration of the symptoms (8.1%), and finally resulted in a progression of CEAP stage (8.5%). The results of this study show that semi synthetic diosmin significantly improves CEAP classification of HVI for patients treated for a month (Table 4, Graph 3), which is more beneficial compared with the research of purified flavonoid fraction⁹. It was also demonstrated that semi synthetic diosmin decreased the capillary filtration rate for patients with HVI, with consequent reduction of oedema and clinical improvement¹².

Also, it was shown that semi synthetic diosmin (7-rhamnoglucoside 5,7,5' – trihydroxy 4-methoxy flavone) had venotonic, vasculoprotective and anti-inflammatory properties^{13,4}, as well as physically or chemically induced effect on capillary resistance^{13, 15}. Anti - oedematous effect is close to anti-inflammatory effect due to inhibition of lipooxygenase, leukocyte migration, and anti-complementary effect^{16,17}. The values of lactate and gas analysis before and after the treatment with semi synthetic diosmin were not significantly changed in the samples of venous blood, even after the static load (Table 5).

TABLE 4

CEAP SLASSIFICATION OF HVI PATIENTS BEFORE AND AFTER TREATMENT WITH SEMI SYNTHTIC DIOSMIN (N=80)

		Before	After
CEAP	1	8	8
	2	16	28
	3	12	9
	4	27	29
	5	15	3
	6	3	3
CEAP ($\bar{x} \pm SD$)		3,40 \pm 1,36	3,00 \pm 1,27
Significance		Z-5,657	p<0,0001

TABLE 5

LEVELS OF LACTATE AND GAS ANALZSIS BEFORE AND AFTER THE ADMINISTRATION OF SEMI SYNTHETIC DIOSMIN IN THE BLOOD SAMPLES TAKEN FORM THE AFFESTEC AND UNAFFECTED LEG, WITH AND WITHOUT STATIC LOAD (n=15)

Biochemical parameters		Before the administration of semi synthetic diosmin				After the administration of semi synthetic diosmin			
		Affected side		Unaffected side		Affected side		Unaffected side	
		0	S	0	S	0	S	0	S
Lactate	X	1,6333	1,9133	1,5667	1,8267	1,4667	1,5800	1,3467	1,3400
	SD	0,8103	0,8184	0,6253	1,0032	0,4155	0,0,4329	0,3739	0,4748
pH	X	7,3487	7,3513	7,3573	7,3560	7,3540	7,3500	7,3567	7,3460
	SD	0,159	0,461	0,890	0,019	0,414	0,330	0,257	0,502
pO ₂	X	4,9733	5,5200	4,1733	4,3333	4,7667	4,6000	5,0600	4,4333
	SD	108813	3,7818	1,0152	1,3621	1,2938	1,4692	1,0815	1,3793
SO ₂	x	64,8000	62,3333	60,0667	58,5333	62,4000	61,6000	67,5333	58,8000
	SD	16,1785	21,8621	16,6153	14,1346	14,4163	14,9609	9,8406	16,6566
pCO ₂	x	6,8400	6,7800	6,7800	6,5467	6,9133	7,0467	6,6267	7,0000
	SD	0,5356	0,5659	0,8152	0,9257	0,5805	0,6010	0,5800	0,6268
TCO ₂	x	29,5067	28,8867	30,0200	307333	29,7867	30,1200	29,9133	30,0200
	SD	2,3545	3,3198	3,2125	2,7907	3,2759	3,4333	2,6936	3,0709

The values of gas analysis and anaerobic metabolites in HVI depended on the stage, etiology, localization (deep, perforating, superficial veins) and pathological finding of obstruction or insufficiency⁸. Thus, for patients with C5-6 EpsAspPr stage of HVI the levels of partial pressure and oxygen saturation were decreased, while the levels of carbon dioxide and bicarbonates were increased, and the values of lactate and pyruvate were not significantly changed. For patients with C5-6 EpsAspPr the signs of hyperoxemia were found, and a local increase of lactate and pyruvate levels occurred at the static load^{8,18}.

The results of this study were made on a heterogeneous group of CEAP classification (average value of C stage before administration of semi synthetic diosmin was 3.40 (Table 4, Graph 3). This explains the fact that it was impossible to demonstrate pathological value of metabolic parameters in such conditions before the administration of the tested drug. Normalization of metabolic parameters after the administration of semi synthetic diosmin could hypothetically be expected only in studies which would include a larger number of patients with venous ulcerations due to various etiologies.

CONCLUSION

The administration of semisynthetic diosmin for 30 days to patients with chronic venous insufficiency resulted in a significant reduction of swelling, pain, and feeling of heaviness and tightness in legs, accompanied with a significant improvement in physical, social, and psychological quality of life, as well as with highly significant improvement of CEAP classification of chronic venous stasis.

SUMMARY

MEDIKAMENTOZNO LEČENJE HRONIČNE VENSKE INSUFICIJENCIJE PRIMENOM SEMISINTETSKOG DIOSMINA – PROSPEKTIVNA STUDIJA

Uvod: Hronična venska insuficijencija (HVI) se manifestuje progresivnim znacima venskog zastoja. Lečenje ovog oboljenja se postiže različitim agensima: kompresivna bandaža, medikamenti, sklerozacija, hirurgija itd.

Cilj rada je prospektivno ispitivanje efekata semisintetskog diosmina (klinički znaci, kvalitet života, lokalni biohemijski parametri) kod bolesnika sa HVI gde nije primenjeno drugo lečenje.

Metod rada Prospektivnom studijom je analizirano 80 bolesnika sa HVI kojima su ispitani faktori rizika i anamnestičke osobine. Dijagnoza HVI je utvrđena na kliničke slike i kolor duplex skena. Pre i 30 dana nakon primene Phlebodia 600^R, kod svih bolesnika su određivani klinički znaci (bol, edem, osećaj težine i raspinja), kvalitet života (fizički, socijalni, psihološki) i CEAP stadijum. Kod 15 bolesnika sa unilateralnim variksima određivane su i lokalne vrednosti laktata i gasnih analiza u uslovima pre i nakon statičkog opterećenja, a kontrolni venski uzorci su uzeti iz zdrave noge. Dobijeni podaci su obrađeni metodama deskriptivne statistike, značajnost neparametarskih obeležja je merena testom Wilcoxonove sume rangova.

Rezultati HVI se nešto češće javlja kod žena nego kod muškaraca, i to na levoj nozi a prosečno u uzrastu 52,3±10,5 godina. Profesije sa statičkim opterećenjem i pozitivna porodična anamneza se često nalaze kod bolesnika sa HVI. Bolesnici su započinjali medikamentozno lečenje prosečno 12,5±8,6 godina od pojave simptoma oboljenja. Značajno kliničko poboljšanje je zabeleženo kod 65/80 ispitanika. Numeričke vrednosti pojedinih kliničkih znakova značajno su niže nakon primene u odnosu na vrednosti pre primene semisintetskog diosmina: otok (0,94:1,50), bol (1,10:1,84), osećaj težine (1,20:1,96) i raspinja (1,14:1,78). Fizički, socijalni i psihološki parametri kvaliteta života su značajno poboljšani nakon primene ispitivanog medikamenta ($p<0,0001$), a to je bilo praćeno i visoko značajnim ($p<0,0001$) popravljanjem CEAP stadijuma HVI (3,00:3,40). Nisu nadjene značajne promene u ispitivanim lokalnim biohemijskim parametrima.

Zaključak Primena semisintetskog diosmina tokom 30 dana dovodi do značajnog poboljšanja kliničkih znakova, kvaliteta življenja i CEAP stadijuma HVI.

Ključne reči: HVI, CEAP, semisintetski diosmin - Phlebodia^R, kvalitet života

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