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EFFICACY OF DRUG THERAPY, SCLEROTHERAPY AND ENDOVENOUS LASER COAGULATION IN THE TREATMENT OF COMORBID CHRONIC HAEMORRHOIDS AND VARICOSE VEINS

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Abstract

Introduction. There is a direct link between the presence in the same patients of chronic haemorrhoids (CH) and varicose veins (VV), and this is especially true for the elderly patients. These nosologies are combined by pathogenesis common links and similar approaches to the treatment. A new term "extended varicose disease" is proposed for these combined comorbid diseases. An individual approach in the treatment of CH can reduce the postoperative wounds healing time by 30% and pain intensity by 3 points, while maintaining the radical intervention. A systematic approach to the treatment helps prevent recurrence of the disease.

The purpose: to evaluate the effectiveness of drug therapy, sclerotherapy and endovenous laser coagulation in CH and VV patients.

Materials and methods. 98 comorbid CH and VV patients, aged 30 - 70 y. o. were under observation. The treatment included back ground drug therapy, endovascular laser coagulation and sclerotherapy.

Results: The effectiveness of CH and VV treatment is manifested by sexual dimorphism in favor of women. Parallel use of *diosmin* positively affects the results ((KW=8,37, p=0,015; τ=+0,161, p=0,019), but the use of *rivaroxaban* (KW=8,87, p=0,012; τ =-0,231, p=0,001) and *heparin* (KW=7,54, p=0,023; χ = -0,265, p<0,001) resulted in the negative. Both after 1 month and after 1 year of follow-up, the effectiveness of sclerotherapy is higher than endovenous laser coagulation ($\chi 2 = 140.76$, $p < 0.001$; $\chi 2 = 14.33$, $p = 0.001$). In stage 1 of treatment, concomitant use of *rivaroxaban* and *heparin* influences its effectiveness (respectively KW = 9.63, p = 0.002 and KW = 18.82, p <0.001), as it is demonstrated by the Kruskel-Wallis analysis.

Conclusions: Optimal medical technology being developed for treatment of combined CH and VV is summarized in the proposed algorithm of surgery. The algorithm developed takes into account the use of drugs, performance of sclerotherapy, endovenous laser coagulation and features and course of the disease, state of vessels endothelial function, and allows to significantly improve the quality of treatment after 1 and 12 months of follow-up and prevents complications.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: *diosmin, rivaroxaban, low molecular weight heparins, chronic haemorrhoids, varicose veins, sodium tetradecyl sulfate, endovenous laser coagulation.*

Introduction

There is a direct link between the presence in the same patients of chronic hemorrhoids (CH) and varicose veins (VV), and this is especially true for the elderly patients. These nosologies are combined by pathogenesis common links and similar approaches to the treatment. A new term "common varicose disease" is proposed to describe these conditions. It should be emphasized that the incidence of HG and VH is constantly increasing [7, 8].

Among non-drug minimally invasive methods of CH and VV treatment sclerotherapy, cryotherapy, laser, galvanic, electrical, bipolar coagulation and radiophotocoagulation [9, 10] is used. It should be noted that after non-surgical treatment of CH grade XIII, recurrences of the disease in 3 months are observed in 13% of cases, and pain persists in 36-49% of the of the patients under observation [11]. There is a combined (laser-sclero-surgical) method of CH treatment. V.A. Musaev (2018) believes that in VV the performance of endovenous laser coagulation (EVLC) and surgical treatment should be completed by sclerotherapy [13]. The use of an individual approach in the treatment of CH can reduce the healing time of postoperative wounds by 30% and reduce the intensity of pain by 3 points, while maintaining the radical intervention. A systematic approach to treatment helps prevent recurrence of the disease [14].

The purpose: to evaluate the effectiveness of drug therapy, sclerotherapy and endovenous laser coagulation in the treatment of comorbid chronic hemorrhoids and varicose veins after 1 and 12 months, as well as to develop an algorithm of rational medical technology and treatment.

Materials and methods

The clinical bases of the study were V. K. Gusak Donetsk Institute of Emergency and Reconstructive Surgery of the National Academy of Medical Sciences of Ukraine, the Donetsk Regional Clinical Territorial Medical Association, Druzhkivka and Kramatorsk (Donetsk region, Ukraine) units of surgery. All the subjects gave informed consent to participate in the examination and processing of their personal data in compliance with moral and ethical principles in accordance with the main provisions of the World Medical Association Declaration of Helsinki (1994, 2000, 2008) and the positive decision of the Commission on Bioethics of the Donetsk National Medical University.

98 comorbid CH and VV patients, aged 30 - 70 y. o. were under observation (the ratio of men and women was 1: 3). Men were significantly older (55.1 ± 1.07 years and 49.6 ± 0.48 years, respectively; t = 5.31, p <0.001). Mean indicators of arterial pressure (MAP) were equal to 107.5 ± 0.68 mm Hg, peripheral vascular resistance (PVR) - 2.7 ± 0.04 2.7 ± din *x* s *x* sm^{-8}, vascular vegetative index (VVI) - 13.0 ± 0.32 r.u.

Hemorrhoidal disease bleeding was classified by 4 variants (types) of severity, according to L. C. Guindic [15]: I - uncommon internal, II - common internal, III - external temporary (transient), IV - external permanent. This 4-point gradation is used to assess the effectiveness of laser coagulation of hemorrhoidal veins [16]. To classify CH patients according to the severity of complications P. A. Clavienet's et al. classification was used [17].

Randomization of VV patients is performed on the diameter of the affected veins (DV) into two types: I - DV <4 mm, which is characterized by swelling of the extremities, hyperpigmentation of the skin and its ulcers, and II type - DV≥4 mm [18]. According to the classification of CEAP (Clinical Etiology Anatomy Pathophysiology), we divided VV patients by degrees of venous insufficiency into two types - moderate (C1-C3) and severe (C4-C6). The exclusion criteria were type I VV patients and C1 for CEAR, and DV averaged 6.6 ± 0.20 mm.

Patients were examined before the treatment, as well as after 1 and 12 months. Informed consent of patients in prospective observations for additional treatment and diagnostic measures was obtained. EVLC was performed under local anesthesia with a solution of lidocaine (at VV - lidocaine + adrenaline + soda) using the device "Photonics-Lika-Surgeon" (Ukraine). EVLC of hemorrhoidal veins was performed at λ = 810 nm, energy power (CL) 5 W, density (EA) 20 J / cm^2, and the lower extremities veins - at λ= 1470 nm, duration of stripping (St) - 30.1 ± 0 , 76 cm, CL - 12,3 ± 0,26 W, total energy of laser output (ΣE) - 1,6 ± 0,04 kJ, energy of output on long stripping (ESt) - 56,2 ± 1,34 J / cm, EA - 29.1 ± 1.17 J / cm^2. In all cases, a tumescent type of fiber was used. EVLC in VV patients was performed by a paravasal "pillow" with Klein's solution using a pump for tumescent anesthesia under ultrasonic control.

For CH and VV sclerotherapy used sclerowein and fibrowein: the first of them is a 0.5-5% solution of polydocanol (daily dose does not exceed 2 mg / kg body weight), and the active substance of fibrowein is sodium tetradecyl sulfate with a concentration of 0.2-3% in 1 ml of the drug. Criteria for exclusion of sclerotherapy were the presence of II-III degrees of respiratory and heart failure, superficial thrombophlebitis with complete obstruction of the deep veins of the leg.

Background drug therapy consisting of diosmin (detralex 1000 mg / day or phlebodia 600 mg / day), rivaroxaban (20 mg once daily or 15 mg twice daily) and / or low molecular weight heparins (cibord 2500 -7500 U, klexan 0.2-0.6 ml). Of the nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors are preferred (meloxicam or movalis 7.5-15 mg / day, arcoxia 60-90 mg / day, nimesil or nimesulide 100-200 mg / day).

Results

71 (72.5%) patients were prescribed diosmin, 19 (19.4%) - rivaroxaban, 25 (25.5%) - low molecular weight heparins, for 56 (57.1%) sclerotherapy of hemorrhoidal veins and veins of the lower extremities was performed, and for others 42 (42,9) EVLC was performed. Sclerotherapy and EVLC patients did not differ in the frequency of use of pathogenetic therapy drugs (Table 1.).

The treatment results were evaluated in a month after sclerotherapy of the veins of the legs or EVLC (1st stage), and in 12 months (2nd stage). Only CH + VV patients were included into the study, they all were observed at both stages. To evaluate the effectiveness of CH treatment the following gradation was used: "significant improvement" (3 points) meant the disappearance of complaints of patients and objective signs of hemorrhoids against the background of any manifestations of treatment complications, a prerequisite for "improvement" (2 points) was reducing the severity of CH or the absence of its objective signs, of course, in the absence of signs of recurrence of the pathological process.

Under "significant improvement" (3 points) of VV we understood disappearance of complaints of patients, reduction of DV in 1 month by 10% and more, and in 12 months of formation of full occlusion of a vessel against any manifestations of treatment complications. A necessary condition of "improvement" (2 points) was a decrease in the degree of venous insufficiency and the creation of segmental occlusion, of course, at the mandatory absence of signs of the pathological process recurrence.

The effectiveness of treatment of CH + VV patients at the 1st stage of observation had certain gender features (in women the results were better; $\chi 2 = 25.19$, $p < 0.001$), but in a year the results were leveled ($\chi 2 = 3.01$, $p = 0.223$). The ratio of slight improvement, improvement and significant improvement in the 1st stage in men was 0: 8: 1, and in women - 1: 15: 7, while in the 2nd stage it was respectively 0: 1: 8 and 1: 4 : 30. In general, among all CH +VV patients, the results of treatment in a month in 1, 2 and 3 points were 3.1%, 72.5% and 24.5%, while in 12 months ($\chi 2 = 426,76$; $p < 0.001$) - 2.0%, 10.2% and 87.8%, respectively (Table 2, Fig. 3-4).

According to Kraskel-Wallis and Kendall analysis the background use of diosmin ($KW = 8.37$, $p = 0.015$; $\tau = + 0.161$, $p = 0.019$) has a positive influence at the results of CH + VV treatment with sclerotherapy in a month; the negative effect has the use of rivaroxaban ($KW = 8.87$, $p = 0.012$; $\tau = -0.231$, $p = 0.001$) and heparin ($KW = 7.54$, $p = 0.023$; $\tau = -0.265$, $p < 0.001$; Fig. 3).

Both in a month and in a year of observation (Fig. 4), the effectiveness of sclerotherapy is higher than EVLC ($\chi 2 = 140.76$, $p < 0.001$; $\chi 2 = 14.33$, $p = 0.001$). At the 1st stage (Fig. 5), concomitant use of rivaroxaban and heparin affected the treatment results (respectively $KW = 9.63$, $p = 0.002$ and $KW = 18.82$, $p < 0.001$), which demonstrates Kruskel-Wallis analysis. The administration of drugs to CH + VV patients at the 1st stage does not affect the results of sclerotherapy (BF = 0.67, p = 0.446) and EVLC (BF = 1.02, p = 0.229).

The effectiveness of treatment of CH + VV patients at the 1st stage of observation weakly correlats with the initial parameters of MAP ($r = -0.154$, $p = 0.129$), PVR ($r = -0.066$, $p = 0.517$) and VVI ($r = -0.019$, $p = 0.854$; Table 3). In a month after surgery (sclerotherapy, EVLC) deterioration of treatment results against a background of arterial primary (essential) hypertension ($D = 5.50$; $p = 0.006$) and diseases of locomotor system (peripheral osteoarthritis, spondyloarthritis,

osteochondrosis of the spine; D = 3.64, p = 0.030) are marked. Diseases of thyroid gland affect the treatment results in 12 months (D = 4.71, p = 0.011); (Table 4).

There are no dispersion-correlation relations of treatment efficacy (Table 5) with the initial state of the vascular endothelial function (VEF) in 12 months. Meanwhile, at the first stage of observation (in a month), the results of treatment are directly correlated with the parameters of prostacyclinemia (D = 3.19, p = 0.046; r = + 0.196, p = 0.048). Taking into account the data of the statistical processing performed a practically directed conclusion was made: in CH + VV patients the blood level of PgI2> 40 ng / ml (> M + SD) is a positive prognosis criterion for further treatment.

At patients with less and higher efficiency of CH + VV treatment (Tab. 6) the absence of differences of initial indicators of VEF is stated at the 1st stage. The differences of three-dimensional integral histograms of vasoconstrictors in the blood of CH + VV patients with different treatment efficiency are presented in Fig. 6.

A factor high values of PSS> 2.7 din x s x sm^{-8} (> M + SD of such patients; PVR = 70.8%) may be used as a sign of negative prognosis regarding sclerotherapy of hemorrhoidal veins and veins of the lower extremities, because there is a reliable dispersion relationship between the effectiveness of therapeutic measures both in the 1^{st} (D = 4.97, p = 0.011) and in the 2^{nd} (D = 3.41, p = 0.040) stage. These data are presented in Table 7.

The results of sclerotherapy of CH + VV patients at the 1st stage of observation are not related to VEF blood initial levels, while at the 2nd stage the effectiveness of treatment directly correlates with the parameter of homocysteinemia (nonparametric criterion of Kendal τ = + 0.250, p = 0.045; Table 8).

The efficiency of EVLC in CH +VV partly depended on the technique of laser ablation (Table 9). Thus, in a month after its implementation, there is a connection with the parameter ESt during exposure to the veins of the lower extremities (D = 7.44, p = 0.002).

According to the multifactor Wilcoxon-Rao analysis, the effectiveness of EVLC of hemorrhoidal veins and veins of the lower extremities with an integrated state of VEF (respectively WR = 6.07, p <0.001 and WR = 2.96, p = 0.013) was revealed at the 2nd stage of observation. As evidenced by one-way dispersion and correlation analyzes of Pearson, the effectiveness of EVLC in CH + VV patients in a month is inversely related (table.10, Fig. 7) with the initial values in the blood VEGF (D = 3.50, p = 0.045; r = -0.336, p = 0.030), and in a year there is a negative relationship with the initial parameter of endothelinemia (D = 3.58, p = 0.046; r = -0.271, p = 0.082).

The results obtained as to effectiveness of sclerotherapy and EVLC at comorbid CH+ VV allowed to make a treatment algorithm that has a practical focus for the surgeons (Fig. 8).

Indicators for sclerotherapy are: 1) the absence of hypertension (MAP <115 mm Hg); 2) the use of background diosmin; 3) blood level PgI2> 40 ng / ml. The indicators of EVLC in such patients include: 1) the use of ESt> 20 J; 2) blood content of VEGF <50 pg / ml

Sclerotherapy of hemorrhoidal veins and veins of the lower extremities is not indicated at PVR > 2.7 din x s x sm^{-8}, and against its background, parallel administration of rivaroxaban and low-molecular-weight heparins to patients is impractical. EVLC planning is excluded in concomitant chronic kidney disease, and is also not recommended in cases of near-opening dilation of the target vein of the lower extremities.

The patients were divided into two groups - the main (1^{st}) and the group of comparison (2^{nd}). The main group consisted of patients with rational approaches to treatment, when sclerotherapy or EVLC was carried out with a short interval of 2 weeks (CH→ VV or VV→ CH), taking into account the recommendations presented in the optimal algorithm (Fig. 8). The individual treatment program took into account the nature of CH and VV, background drug therapy, comorbidities, laser ablation techniques and the initial state of VEF.

As it is seen from Fig. 9, the effectiveness of treatment of patients in the main group was significantly higher in both the first and second stages of observation (respectively 3.2 times, $\chi 2$ = 74.30, p <0.001 and 15%, $\chi 2$ = 13.78, p = 0.002). In the main group, there were no recurrences of CH and VV, while in 12 months they were observed in the group of comparison in 3.3% of cases.

In the 1st group complications of sclerotherapy and EVLC at the stages of observation occurred only

in one case (paresthesia), while in the comparison group theym were 5.8 times more often ($\chi 2 = 3.88$, $p = 0.049$), in particular, hyperpigmentation of the skin was found in 5.0% of patients, respectively paresthesia and phlebitis - in 3.3%, deep vein thrombosis and perianal eczema - in 1.7% ($\chi 2 = 11.15$, $p = 0.025$). These results allow to confirm the advantages of the medical technology developed at the presence of comorbid CH and VV.

Conclusions

The effectiveness of treatment of combined pathology, namely chronic haemorrhoids and varicose veins is manifested by sexual dimorphism in favor of women.

Concomitant use of diosmin (but not rivaroxaban or low molecular weight heparins) positively affects it, and in a month after surgery, sclerotherapy is preferable. In a year endovenous laser coagulation, which is negatively affected by the class of venous insufficiency and near-opening dilation of the target vein of the lower extremities at their varicose, high levels of peripheral vascular resistance, concomitant primary hypertension, chronic kidney disease, thyroid and musculoskeletal disorders, imbalance of vasoconstrictors and vasodilators of vascular endothelial function.

The optimal medical technology for the treatment of combined chronic hemorrhoids and varicose veins is summarized in the proposed algorithm of surgery performance. The latter takes into account the use of drugs, performance of sclerotherapy and endovenous laser coagulation, features of the disease's course and its nature. This approach significantly improves the quality of treatment in a month and a year of follow-up and prevents complications.

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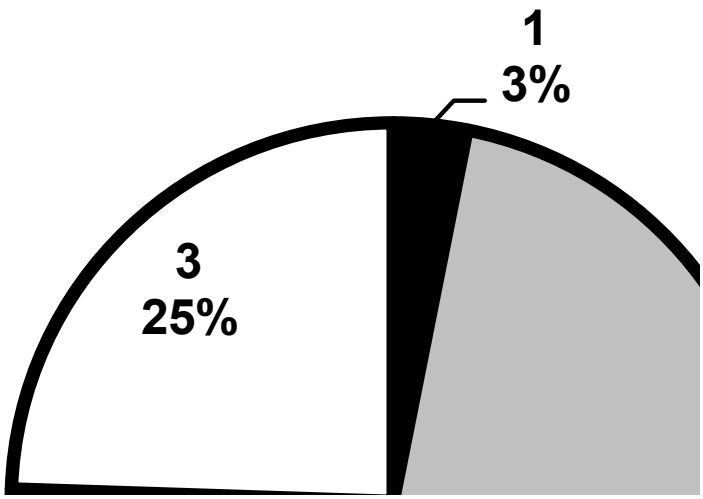
References

1. Vessey M, Yeates D. Varicose veins and haemorrhoids: findings in the Oxford-FPA study. J Fam Plann Reprod Health Care 2018;38(1):63-9.
2. Yetkin E. Hemorrhoid, internal iliac vein reflux and peripheral varicose vein: Affecting each other or affected vessels? Phlebology 2018;30(2):145-9.
3. Ekici U, Kartal A, Ferhatoglu MF. Association between hemorrhoids and lower extremity chronic venous insufficiency. Cureus 2019;11(4):4502.
4. Sutzko DC, Obi AT, Kimball AS, Smith ME, Wakefield TW, Osborne NH. Clinical outcomes after varicose vein procedures in octogenarians within the vascular quality initiative varicose vein registry. J Vasc Surg Venous Lymphat Disord 2018;6(4):464-70.
5. Khojasteh A, Sanchez-Muñoz R, Moyano E, Bonfill M, Cusido RM, Eibl R. Biotechnological production of ruscogenins in plant cell and organ cultures of Ruscusaculeatus. Plant Physiol Biochem 2019;141(8):133-41.
6. Yetkin E, Ileri M. Dilating venous disease: pathophysiology and a systematic aspect to different vascular territories. Medical Hypotheses 2016;91(6):73-6.
7. Lohsiriwat V, Scholefield JH, Dashwood MR, Wilson VG. Pharmacological characteristics of endothelin receptors on sheep rectal blood vessels. Pharmacol Res 2017;63(3):490-5.
8. Brodovskyi SP, Iftodiy AG, Kozlovska IM. Optimization of surgical treatment of hemorrhoidal disease stages III-IV. KlinKhir 2017;(2):10-2.
9. Nikshoar MR, Maleki Z, NematiHonar B. The clinical efficacy of infrared photocoagulation versus closed hemorrhoidectomy in treatment of hemorrhoid. J Lasers Med Sci 2018;9(1):23-6.
10. Pesta W, Wirkowski A, Leksowski K. Stapled haemorrhoidopexy for the treatment of haemorrhoids: a review of our experience. Videosurg Miniinv 2019;4(4):147-53.
11. Naderan M, Shoar S, Nazari M, Elsayed A, Mahmoodzadeh H, Khorgami Z. A randomized controlled trial comparing laser intra-hemorrhoidal coagulation and Milligan-Morgan hemorrhoidectomy. J Invest Surg 2017;30(5):325-31.
12. Rodoman GV, Kornev LV, Shalaeva TI, Malushenko RN. Efficiency of combined methods of hemorroid treatment using hal-rar and laser destruction. Khirurgiia 2017;(5):47-51.
13. Musaev V.A. Final sclerotherapy of recurrent and residual varicose veins of the lower extremities after surgical and endovenous treatment. Klin Khir 2018; 85 (11): 40-3.

14. Tutchenko MI, Andriyets VS, Ayman Alvan Jafar, Symonenko SO, Khmelyar IV, Melikov ZA. Individual approach in the treatment of chronic hemorrhoids. Klin Khir 2016; 10.3 (Appendix): 136.
15. Guindic LC. Treatment of uncomplicated hemorrhoids with a Hemor-Rite® cryotherapy device: a randomized, prospective, comparative study. J Pain Res 2014;16(7):57-63.
16. Giamundo P, Braini A, Calabro G, Crea N, De Nardi P, Fabiano F et al. Doppler-guided hemorrhoidal dearterialization with laser (HeLP): a prospective analysis of data from a multicenter trial. Tech Coloproctol 2018;22(8):635-43.
17. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250(2):187-96.
18. Radhakrishnan N, George D, Jayakrishnan R, Sumi S, Kartha CC. Vein size and disease severity in chronic venous diseases. Int J Angiol 2018;27(4):185-9

Table 1. Frequency of the drugs use in pathogenic therapy of CH + VV patients at the background of sclerotherapy and EVLC

Drugs	Groups of patients				Differences of groups	
	At sclerotherapy, n=56		At EVLC, n=42			
	Abs	%	Abs	%	$\chi 2$	P
Diosmin	39	69.6	32	76.2	0.52	0.473
Ribaroxaban	9	16.1	10	23.8	0.92	0.338
Heparin	13	23.2	12	28.6	0.36	0.547



In a month in 12 months

Figure. 1. The effectiveness of CH + VV patients treatment in a month and a year after sclerotherapy or EVLC. Efficacy of treatment: 1 - slight improvement, 2 - improvement, 3 - significant improvement.

Table 2. The effectiveness of CH + VV treatment at the first (in a month) and the second (in 12 months) stages of the patients examination

STAGE	Gender of patients	Effectiveness of treatment					
		1 - slight improvement		2 - improvement		3 - significant improvement	
		Abs	%	Abs	%	Abs	%
In amonth	Male	-	-	25	89.3	3	10.7
	Female	3	4.3	46	65.7	21	30.0
In 12 months	Male	-	-	3	10.7	25	89.3
	female	2	2.9	7	10.0	61	87.1

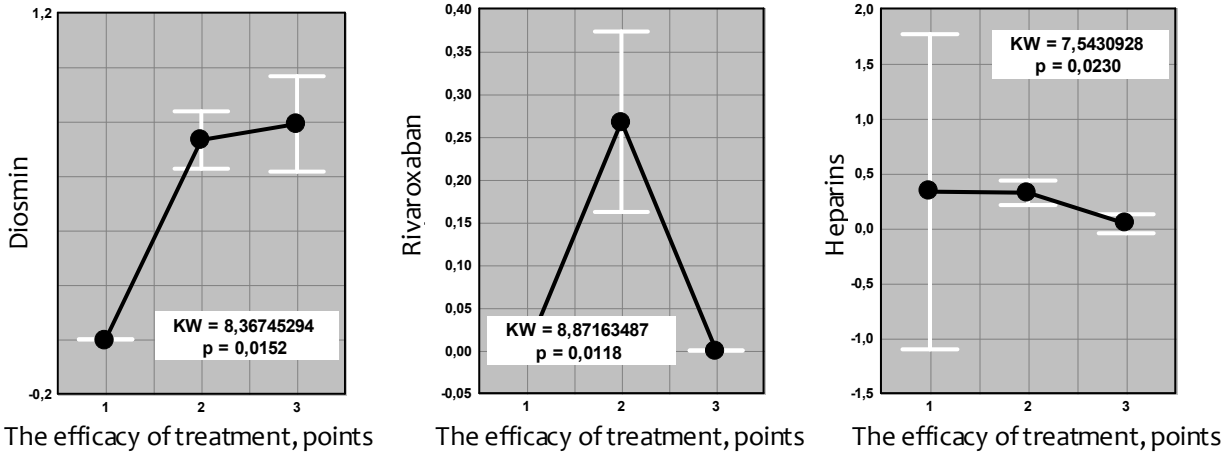
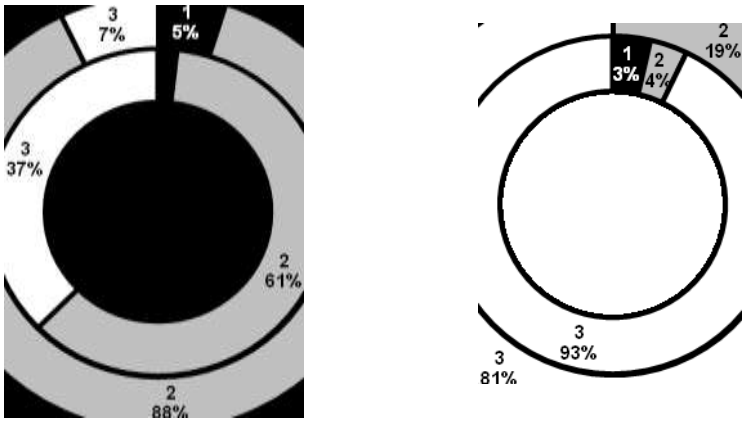


Figure 3. The degree of influence of various drugs on the effectiveness of sclerotherapy and EVLC in CH + VV patients (Kraskel-Wallis test).



In a month in 12 months

Figure 4. Comparative effectiveness of sclerotherapy and EVLC in CH + VV patients in a month and 12 months.
Note. The inner circle - sclerotherapy, the outer circle - EVLC.

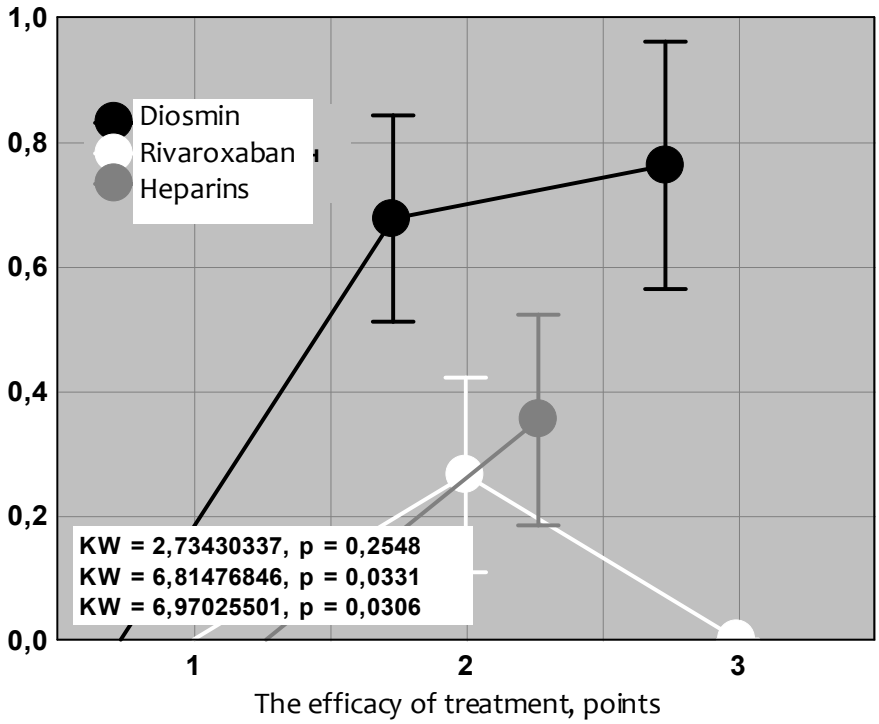


Figure 5. Influence of various drugs on the effectiveness of sclerotherapy in CH + VV patients (Kraskel-Wallis test).

Table 3. Correlation-regression relationships between the effectiveness of CH + VV patients treatment with initial indexes of arterial vessels

Factors	Correlation in a month		influence			
			In a month		In 12 months	
	R	P r	D	pD	D	pD
MAP	-0.154	0.129	1.73	0.184	1.01	0.370
PVR	-0.066	0.517	1.59	0.210	1.77	0.177
VVI	-0.019	0.854	0.10	0.908	0.45	0.639

Table 4. Influence of concomitant pathology on the effectiveness of CH + VV patients treatment

Nosology	Term of observation			
	In a month		in 12 months	
	D	P	D	p
Atherosclerosis of the vessels of the legs	1.93	0.151	0.40	0.671
Coronary heart disease	0.69	0.506	0.85	0.432
Hypertension	5.50	0.006	0.49	0.616
Diabetes	0.78	0.460	0.30	0.744
Diseases of locomotor system	3.64	0.030	0.73	0.483
Diseases of the digestive system	0.45	0.639	0.35	0.703
Diseases of the respiratory system	0.83	0.441	0.77	0.468
Chronic hepatitis	0.21	0.812	0.43	0.648
Chronic kidney disease	1.07	0.346	0.10	0.902
Thyroid disease	0.14	0.872	4.71	0.011

Table 5. Dispersion-correlation relations of efficacy of HC + VV patients treatment with initial indicators of vascular endothelial function (VEF)

VEF	Term of observation							
	In a month				In 12 months			
	Influence		Correlation		Influence		correlation	
	D	pD	R	Pr	D	pD	r	Pr
VEGF	1.35	0.265	-0.110	0.279	0.01	0.997	+0.008	0.939
ET1	0.72	0.489	-0.063	0.540	1.28	0.284	-0.118	0.248
HC	0.60	0.551	-0.024	0.817	0.61	0.547	+0.069	0.499
TxA2	0.06	0.943	-0.033	0.746	1.00	0.372	-0.002	0.985
Pg12	3.19	0.046	+0.196	0.048	0.09	0.918	+0.019	0.853

Table 6. Initial VEF indicators in CH + VV patients with different treatment efficacy (M ± SE)

Indicators	treatment effectiveness		Group differences	
	< points	3 points	T	p
VEGF, pg/ml	87.94.27	82.6±7.91	0.58	0.566
ET1, pg/ml	5.7±0.19	5.4±0.35	0.95	0.347
HC, mkmol/l	16.2±0.44	16.4±0.57	0.17	0.869
TxA2, ng/ml	13.4±0.75	12.9±1.22	0.35	0.730
PgI2, ng/ml	25.2±2.44	28.2±1.39	1.06	0.290

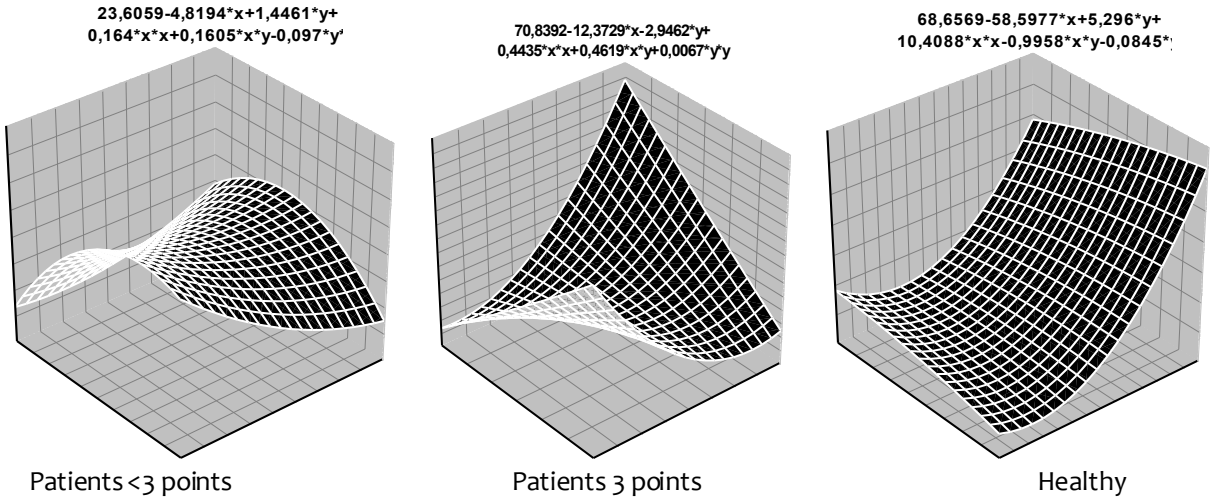


Figure 6. Initial three-dimensional integral histograms of vasoconstrictors indicators (ET1 + HC + TxA2) in CH + VV patients with various efficiency of treatment and at healthy persons.

Table 7. Correlation-regression relationships between the effectiveness of sclerotherapy in CH + VV patients with initial indexes of arterial vessels

Factors	Correlation in a moth		Influence			
			In a month		In 12 months	
	R	pr	D	pD	D	pD
MAP	-0.182	0.180	1.14	0.327	1.38	0.261
PVR	-0.169	0.214	4.97	0.011	3.41	0.040
VVI	-0.195	0.150	1.27	0.288	1.98	0.148

Table 8. Dispersion-correlation relations of sclerotherapy efficiency in CH + VV patients with initial indicators of VEF

VEF	Terms of observation							
	In a month				In 12 months			
	Influence		Correlation		Influence		Correlation	
	D	pD	T	p τ	D	pD	T	p τ
VEGF	0.39	0.680	+0.009	0.950	0.06	0.938	-0.021	0.879
ET1	1.23	0.300	-0.074	0.586	0.18	0.838	+0.022	0.875
HC	0.10	0.907	0.052	0.706	1.53	0.225	+0.250	0.045
TxA2	0.22	0.807	-0.082	0.546	0.47	0.626	+0.132	0.331
Pgl2	1.47	0.240	+0.145	0.288	0.48	0.622	-0.061	0.658

Table 9. Correlation-regression relationships between the effectiveness of treatment of CH +VV patients with indexes of EVLC

EVLC indications	Correlation in amonth		Influence			
			In a month		In 12 months	
	r	Pr	D	pD	D	pD
St	-0.032	0.843	3.00	0.061	0.37	0.547
CL	+0.066	0.678	1.46	0.245	0.02	0.903
Σ St	+0.123	0.437	1.39	0.261	0.21	0.649
ESt	+0.016	0.464	7.44	0.002	0.54	0.465
EA	-0.027	0.863	3.06	0.058	0.03	0.872

Table 10. Dispersion-correlation relations of EVLC efficacy in CH + VV patients with initial VEF values

VEF	Term of observation							
	In a month				In 12 months			
	Influence		Correlation		Influence		Correlation	
	D	pD	R	Pr	D	pD	r	Pr
VEGF	3.50	0.045	-0.036	0.030	3.11	0.742	+0.052	0.742
ET1	0.01	0.091	+0.018	0.910	3.58	0.046	-0.271	0.082
HC	1.02	0.371	-0.216	0.169	0.78	0.383	-0.138	0.383
TxA2	0.07	0.932	-0.021	0.893	0.52	0.477	-0.113	0.477
PgI2	1.57	0.222	-0.159	0.314	0.34	0.565	+0.091	0.565

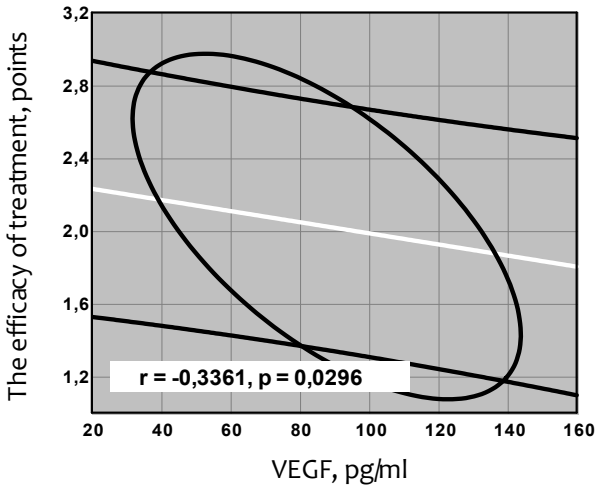


Figure 7. Correlation of Pearson's effectiveness of CH + VV patients treatment in a month of observation after EVLC with initial VEGF indexes in the blood.

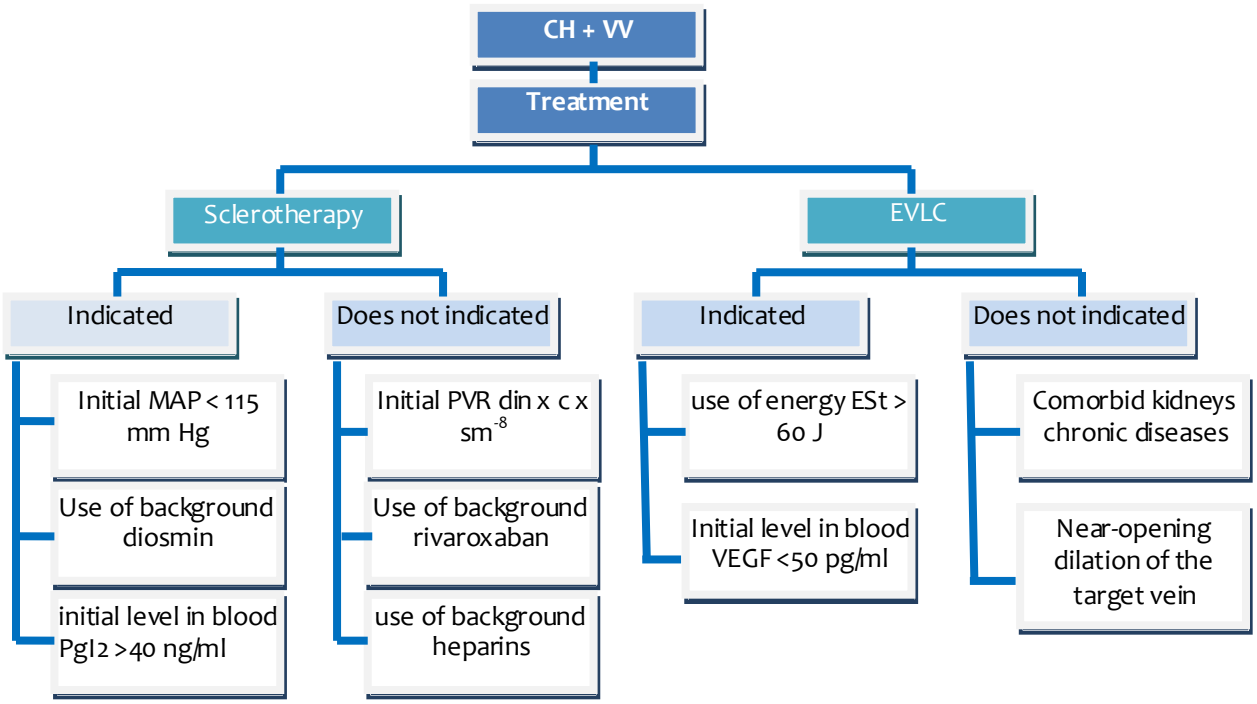


Figure 8. Algorithm of CH + VV optimal treatment

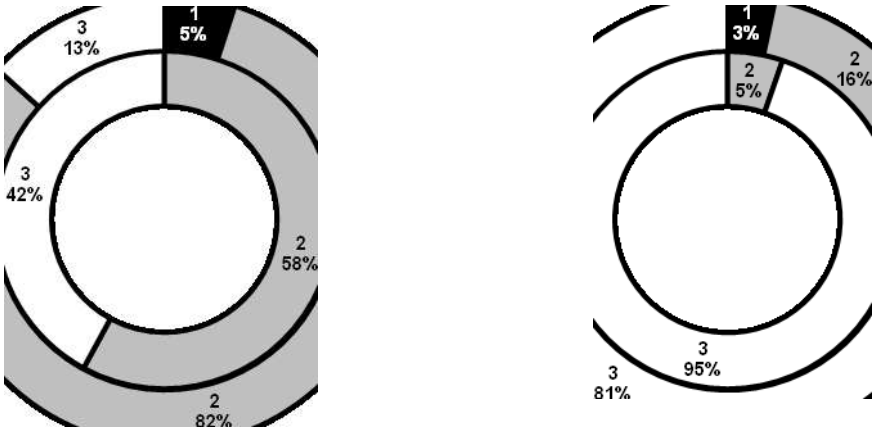


Figure 9. The effectiveness of CH + VV patients treatment in a month and 12 months.
Note. The inner circle is the main group, the outer circle is the group of comparison.