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Original Article

Drug correction of endothelial dysfunction after operations for varicose veins

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Abstract

Endothelial dysfunction is one of the key points in the development of varicose veins in the lower extremities—the aim of the study. To determine the presence of endothelial dysfunction in the early and late postoperative period and to carry out its medical correction. Markers of endothelial dysfunction, in particular, P-selectin, E-selectin, tissue plasminogen activator, endothelin-1, vascular endothelial adhesion molecule type 1 and circulating endothelial cells were determined in patients with varicose veins operation. It has been established that indicators of endothelial dysfunction markers increase in the early postoperative period. After 60 days after surgical interventions, signs of endothelial dysfunction remain, although according to the analysis of indicators, it is lower than in the early postoperative period. At the same time, after analyzing the indicators obtained after the operation, we can conclude that using only diosmin with hesperidin reduces endothelial dysfunction in the early and late postoperative period but does not completely eliminate it. Combining diosmin with hesperidin and quercetin enhances their effect in the distant postoperative period, significantly reducing endothelial dysfunction indicators. After operations for varicose veins of the lower extremities, the manifestations of endothelial dysfunction persist, requiring medical correction. The combination of flavonoids diosmin + hesperidin + quercetin can be used to correct endothelial dysfunction in the early and late postoperative period.

Keywords: varicose veins, postoperative period, endothelial dysfunction, correction

Introduction

It is generally accepted that varicose is a multifactorial disease whose pathophysiology is inflammation caused by persistent venous hypertension and valvular insufficiency [1, 2]. Changes in shear stress are directly perceived by endothelial cells, which leads to their activation and subsequent recruitment of leukocytes and the release of proinflammatory agents [3]. Dysfunctional endothelium plays a key role in maintaining the inflammatory cascade with subsequent pathological venous changes and worsening of chronic venous disease [4]. Thus, analyzing modern scientific literature, it can be considered that endothelial dysfunction is one of the key points in the development of varicose veins of the lower extremities [5, 6]. It should also be noted that operations for varicose veins do not solve the problem of endothelial dysfunction in the postoperative period. In recent years, scientific publications have claimed the presence of endothelial dysfunction after surgery for varicose veins of the lower extremities.

Despite thorough research into the causes of the development of varicose veins, its pathophysiological aspects remain unclear, which makes it difficult to prescribe appropriate drug therapy [7, 8].

To establish the presence of endothelial dysfunction in the early and late postoperative period and to carry out its correction.

Material and methods

Endothelial dysfunction (ED) was assessed by determining the level of endothelial dysfunction markers: P-selectin, E-selectin, tissue plasminogen activator, endothelin-1, vascular endothelial adhesion molecule type 1, and circulating endothelial cells (ECC). These indicators were studied after endovenous laser ablation (EVLA) of veins in 60 patients (1 day before surgery, 10 and 60 days after surgery). The control was 30 healthy people. We also determined ED in 34 patients who took diosmin with hesperidin and 30 patients who took diosmin with hesperidin and quercetin in the postoperative period. We also determined ED in 34 patients who took diosmin with hesperidin in the postoperative period and 30 patients who were prescribed diosmin with hesperidin and quercetin.

Blood sampling was carried out intraoperatively by puncturing the ulnar vein of the forearm and the trunk of the varicose-dilated large saphenous vein, departing from the saphenous-femoral junction distally by 2 cm.

Concentrations of P-selectin, E-selectin, tissue plasminogen activator, type 1 vascular endothelium adhesion molecule (sVCAM-1-soluble vascular cellular molecule) were determined using kits from Bender MedSystems (Austria) for enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. The concentration of endothelin-1 was determined using kits from the company "Biomedica" (Canada) for ELISA according to the manufacturer's instructions. Reaction evaluation was performed on a SUNRISE microplate semi-automatic photometer (Tecan, Austria) using a Hydroflex wash station (Tecan, Austria), allowing for standardization of these methods.

To determine the circulating endothelial cells (CEC), we used the method of J. Hladovec [9] in modification N.N. Petrishcheva *et al.* [10]. Also, blood for research in the postoperative period was collected from the femoral vein of the limb by its puncture and from the ulnar vein of the forearm.

The obtained results were analyzed using the STATISTISA 12.0 program package. The significance of the obtained differences between the results (minimum level of significance $p<0.05$) was evaluated using the Kruskel-Wallace and Newman-Keuls tests (BioStat program, AnalystSoft Inc.).

Results

Our studies of the state of the endothelial system after EVLA show, however, that after EVLA, on the 10th day, there is (Table 1) an increase in CEC from (7.13±1.72) cells ×104/l to (9.53±1.96) cells ×104/l ($p<0.05$)

Also, on the 10th day, an increase in sVCAM-1 was noted from (356.76±4.7) ng/ml to (477.4±8.9) ng/ml, which is 1.93 times higher than the indicator of the control group and 1, 34 times the original indicator ($p<0.05$) (Table 2).

Analyzing the obtained indicators after performing EVLA, we can conclude that using only diosmin with hesperidin reduces endothelial dysfunction in the early and late postoperative period but does not completely eliminate it (Table 3).

Discussion

The increased concentration of sVCAM-1 after surgery also indicates increased adhesion of leukocytes to endothelial cells as a reaction to traumatization of the venous wall.

When analyzing the level of P-selectin, a slight increase in its concentration is noted from (161.9± 2.7) ng/ml

Table 1: Comparative characteristics of ED indicators before surgery and in the postoperative period during endovenous laser coagulation (n=60).

Indicator	Control (n=30)	Before surgery	10 days after surgery	60 days after surgery
CEC, cells ×104/l	4.3±1.2	7.13±1.72*	9.53±1.96*	6.13±1.09*
sVCAM-1, ng/ml	234.2±7.6	356.76±4.7*	477.4±8.9*	292.57±24.13*
P-selectin, ng/ml	161.9±2.7	201.7±2.4*	183.1±3.7*	157.57±7.35*
E-selectin, ng/ml	39.6±4.6	47.9±5.2*	46.4±4.0*	25.26±3.0*
Endothelin-1 pmol/ml	2.2±0.4	3.0±1.2*	2.78±0.28*	2.46±0.24*
		* – $p<0.05$		

Table 2: The results of the study of biochemical markers of endothelial dysfunction in patients with varicose veins after surgery using diosmin with hesperidin (n=34).

Indicator	Control (n=30)	Before surgery	10 days after surgery		60 days after surgery	
			EVLA	EVLA diosmin with hesperidin	EVLA	EVLA diosmin with hesperidin
CEC, cells ×104/l	4.3±1.2	7.13±1.72*	9.53±1.96*	8.45±2.96*	6.13±1.09*	5.44±1.79*
sVCAM-1, ng/ml	234.2±7.6	356.6±4.7*	477.4±8.9*	401±3.6*	292.57±2.3*	253±2.6*
P-selectin, ng/ml	161.9±2.7	201.7±2.4*	183.1±3.7*	171.5±3.3*	167.7±3.12*	164.3±2.9
E-selectin, ng/ml	39.6±4.6	47.9±5.2*	46.4±4.0*	43.2±2.09*	42.6±3.0*	40.6±2.3*
Endothelin-1, pmol/ml	2.2±0.4	3.0±1.2*	2.78±0.28*	2.64±1.3*	2.46±0.24*	2.34±0.5

* – p<0.05

before surgery to (183.1±3.7) ng/ml on the 10th day after minimally invasive intervention. E-selectin before surgery is (47.9±5.2) ng/ml (p<0.05), on the 10th day after EVLA – (46.4±4.0) ng/ml (p<0.05). The concentration of endothelin-1 on the tenth day after EVLA is (2.78±0.28) ng/ml (p<0.05), at (2.24±0.4) ng/ml (p<0.05) in the control group.

After 60 days after surgical interventions, signs of ED remain, although according to the analysis of indicators, it is lower than in the early postoperative period. Thus, after EVLA, the number of CECs remains higher than the control indicators – (6.13±1.09) cells ×104/l, with controls – (4.3±1.2) cells ×104/l (p<0.05). A similar picture was observed with the concentration of sVCAM-1. On the 60th day after minimally invasive surgical intervention, the concentration of this marker is (292.57±24.13) ng/ml. At the same time, the control is (234.2±7.6) ng/ml, which is 1.8 times lower than the 10-day indicator of this group (p<0.05).

Thus, regardless of surgical intervention aimed at eliminating varicose veins of the lower extremities, endothelial dysfunction persists both in the early and late postoperative period.

This phenomenon can be explained by the existing and uncorrected morphofunctional changes in the venous wall of the deep venous system, which were revealed during our morphological studies. In particular, the progression of these changes in the deep venous system, especially at the endothelial and subendothelial layers level in the postoperative period, maybe one of the reasons for the postoperative recurrence of varicose veins [11]. Multicomponent drug therapy is necessary to reduce the manifestations of endothelial dysfunction in the postoperative period.

For this purpose, in 34 patients, we used a combination of micronized purified flavonoid fraction, which contains 900 mg of diosmin (90%) and 100 mg of flavonoids in the form of hesperidin, 1 capsule 1 time

Table 3: The results of the study of biochemical markers of endothelial dysfunction in patients with varicose veins before surgery and after surgery with the complex use of diosmin with hesperidin and quercetin (n=30).

Indicator	Control (n=30)	Before surgery	10 days after surgery		60 days after surgery	
			EVLA	EVLA diosmin with hesperidin and quercetin	EVLA	EVLA diosmin with hesperidin and quercetin
CEC, cells ×104/l	4.3±1.2	7.13±1.72*	9.53±1.96*	6.5±1.3*	6.13±1.09*	5.02±1.1*
sVCAM-1, ng/ml	234.2±7.6	356.6±4.7*	477.4±8.9*	326.2±3.2*	292.57±2.3*	264.2±1.7*
P-selectin, ng/ml	161.9±2.7	201.7±2.4*	183.1±3.7*	185.7±9.3*	167.7±3.12*	165.3±1.5*
E-selectin, ng/ml	39.6±4.6	47.9±5.2*	46.4±4.0*	42.9±0.9*	42.6±3.08*	40.5±3.2*
Endothelin-1, pmol/ml	2.2±0.4	3.0±1.2*	2.78±0.28*	2.44±0.13	2.46±0.24*	2.31±0.7*

* – p<0.05

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a day for a week before surgery and 3 months after surgery. We have considered that diosmin with hesperidin statistically significantly increases the elasticity coefficient, indicating its tonic effect on the vein wall. Diosmin with hesperidin also has a pronounced anti-inflammatory effect, blocking the synthesis of prostaglandins PGE 2, PGE 2ct, and thromboxane B, which significantly reduces the permeability of microcirculatory vessels, increases capillary resistance, and improves lymphatic drainage. These drugs inhibit the adhesion and migration of neutrophil leukocytes to the vein wall (L-selectin) and endothelial (ICAM-1, VCAM-1) adhesion molecules. The combination of these drugs also effectively protected endothelial cells and the extracellular matrix from chemical mediators of inflammation. In order to determine the effectiveness of the above-mentioned combination of drugs, we analyzed the indicators characterizing the state of the endothelial system after EVLA.

Considering analyzing the obtained indicators after performing EVLA, we used a combination of diosmin with hesperidin and quercetin in 30 patients, taking into account the peculiarities of the pharmacological action of the latter, which in many components does not overlap with the action of diosmin with hesperidin. Thus, based on literature data, we have considered that quercetin eliminates refraction of the endothelium and edema of the intima, blocking the production of adhesive molecules by the endothelium activated by liposaccharides. The drug also blocks the activity of proteinase C, one of the components of the poly phosphoinositide system of intracellular signal transmission, through which the activating effect on the endothelium is realized. Also, quercetin has been noted to have a protective effect on the endothelium when it is damaged by angiotensin II, as well as on the content in the blood of a marker of endothelial dysfunction – Willibrand factor. In addition, quercetin performs the function of stabilizing endotheliocyte membranes, inhibiting oxygenase enzymes and degradation of basal membranes (phospholipid biolayer of membranes), reduces the accumulation of neutrophils, and also reduces the concentration of biologically active substances (leukotrienes, lipoxins, lysophospholipids). Thus, quercetin has a multidirectional multicomponent effect, which combines endothelioprotective, anti-inflammatory and proto-edematous effects [12, 13].

Quercetin was prescribed together with diosmin and hesperidin at a dose of 40 mg twice a day. Patients took this combination of drugs 2 times a day, a week before the operation and 3 months after it.

Analyzing indicators of ED markers in the postoperative period, it can be stated that using a combination of diosmin preparations with hesperidin and quercetin already on the 10th day after surgery contributes to their gradual reduction. It is necessary to pay attention to the fact that during the following months after the operation, the strengthening of the effect of these drugs on the manifestations of ED is noted. This is evidenced by the fact that 60 days after the operation, after complex corrective treatment with diosmin, hesperidin and quercetin, the CEC values practically approached the norm – (5.02±1.1) cells ×104/l against (4.3±1.2) cells ×104/l. A similar situation is observed with other ED markers. Thus, the indicators of sVCAM-1, P-selectin, E-selectin, and Endothelin-1 significantly decreased compared to the control (264.2±1.67) ng/ml, (165.3± 1.5) ng/ml, (40.5±3.2) ng/ml, (2.31±0.7) pmol/ml.

Thus, it is possible to ascertain the strengthening of the effect of the combination of diosmin with hesperidin and quercetin on ED, which manifests itself with an increase in the duration of the postoperative period.

Conclusion

After operations for varicose veins of the lower extremities, the manifestations of endothelial dysfunction persist, requiring medical correction. The combination of flavonoids diosmin, hesperidin, and quercetin can be used to correct endothelial dysfunction in the early and late postoperative period.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The Ethics Committee of the Meeting of the Bioethics Commission of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine approved this study (approval ID: 66a/ November 01/2023).

Consent to participate

Written informed consent was obtained from all the participants.

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