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ORIGINAL ARTICLE

Benefits of micronized purified flavonoid fraction as adjuvant therapy on inflammatory response after sclerotherapy

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ABSTRACT

BACKGROUND: Sclerotherapy is the treatment of choice for telangiectasias. The aim of this study was to investigate the systemic and local inflammatory response after sclerotherapy in women with chronic venous disease (CVD) and to assess the effects of micronized purified flavonoid fraction (MPFF) in combination with sclerotherapy on markers of inflammation and endothelial dysfunction.

METHODS: Sixty women with primary CVD CEAP class C_1 were randomly assigned sclerotherapy in combination with MPFF treatment (N=30) or sclerotherapy alone (control) group (N.=30). In the treatment group, patients received MPFF tablets 1000 mg daily for 2 weeks before the scheduled sclerotherapy and for at least 2 months after the procedure. Microsclerotherapy was performed according to standard protocol using modern sclerosing agents. Blood samples were collected from the central vein of the target vascular cluster before and 10 days after sclerotherapy to evaluate markers of inflammation and endothelial dysfunction including: C-reactive protein within the high-sensitivity range, histamine, interleukin-1, tumor necrosis factor-alpha, and vascular endothelial growth factor. To measure the systemic inflammatory response, blood samples were also collected from the forearm vein in 15 control patients.

RESULTS: Baseline levels of markers of inflammation and endothelial dysfunction obtained from the central vein of the treatment site showed no statistically significant differences between treatment groups. In both groups, all markers were significantly increased 10 days after sclerotherapy. In the control group, the same markers obtained from the forearm were not modified 10 days after sclerotherapy indicating the inflammatory reaction was local and not systemic. MPFF treatment reduced all markers of inflammation and endothelial dysfunction compared with the control group.

CONCLUSIONS: Prescription of MPFF starting prior to sclerotherapy and throughout the post-operative period reduced the vein-specific pro-inflammatory reaction and may thereby reduce the unwanted side effects of sclerotherapy and improve treatment outcomes.

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Key words: Flavonoids - Inflammation - Sclerotherapy.

Sclerotherapy or endovenous chemical ablation is the targeted chemical ablation of varicose veins by intravenous injection of a sclerosing drug.[1, 2] It is the most popular procedure for elimination of dilated intradermal veins and telangiectasias due to its technical simplicity, good tolerability, minimal downtime, and low cost. The aim is to cause irreversible endothelial injury in the desired vessels while avoiding damage to normal collateral vessels and surrounding tissues. A vein-sclerosing agent (sclerosant) is injected into the target vein, causing damage to the endothelial and subendothelial layers and an inflammatory reaction of the venous wall.[3, 4] This results in the formation of a dense clot (sclero-thrombus), transformation of the vessel into a fibrous cord, and, eventually, involution of the connective tissue of the target vein. The probability of such an outcome is increased with the additional use of compression treatment (bandages and hosiery).[5, 6]

The subtler mechanisms of the impact of vein-sclerosing agents on the venous wall, such as effects on blood cells and proteins, as well as on perivascular tissues, have been assessed in a number of *in-vitro and in-vivo* studies.[3, 7-11] The results indicate that all vein-sclerosing agents, independent of their chemical nature,

concentration, aggregate state and route of administration, induce a varying degree of inflammation to the venous wall, which in some cases also extends to the perivascular structures. Moreover, the induced inflammation is thought to be a factor in the development of common sclerotherapy adverse events, such as hyperpigmentation, neovasculogenesis and persisting phlebitis, with a rate of 75-80%, even with the use of modern vein-sclerosing agents.[12]

With the widespread use of vein-sclerosing treatment in clinical practice, there is a parallel search for methods to ameliorate or prevent the treatment-associated adverse events. A number of options have been proposed including long-term compression treatment,[5, 6] antihistamines, topical corticosteroids, heparin-containing gels, pentoxifylline derivatives, and nonsteroidal anti-inflammatory drugs (NSAIDs).[13]

The presence of acute venous endotheliopathy induced by vein-sclerosing agents, suggests that venoactive (phlebotropic) drugs inhibiting leukocyte-endothelial interaction, a key component of vein-specific inflammation, may play a beneficial role in modulating this process and decreasing the risk of undesired side effects.[14] This hypothesis has been indirectly demonstrated in previous studies, where administration of micronized purified flavonoid fraction (MPFF; Detralex, Servier, Russia) during the periprocedural period improved outcomes of open surgery and endovascular interventions for varicose disease of the lower extremities.[15-18]

The aim of the current study was to assess the degree of systemic and local inflammatory response after sclerotherapy and the beneficial effects of MPFF.

Materials and methods

The study enrolled 60 women aged from 18 to 35 years (mean age 27.4±4.5 years) with primary chronic venous disease (CVD) of C_1 class according to the CEAP classification (reticular veins and/or telangiectasias) [19] and a body mass index (BMI) not greater than 25 kg/m^2. The principal inclusion criterion to ensure standardization of conditions for the procedure was the presence of reticular veins and/or telangiectasias on the outer thigh (fan pattern) (Figure 1). Exclusion criteria were as follows: valvular incompetence of the superficial conduit veins and their tributaries according to duplex ultrasound data; treatment with nonsteroidal anti-inflammatory drugs; antihistamines; sex hormone preparations; or concomitant diseases accompanied by a systemic or local inflammatory response.

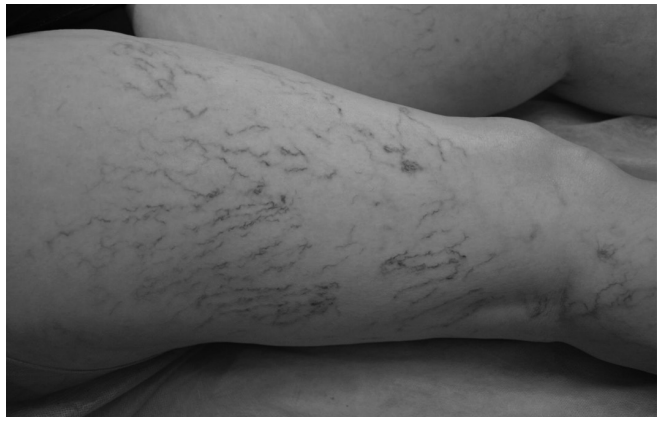

Figure 1.—Reticular veins and telangiectasias on the outer thigh.

The protocol and design of study were approved by the local ethics committee of the Russian National Research Medical University named after N.I. Pirogov (Chairmen Storozhakov G.I.) (Extract from the Protocol No. 143 dd. 26.09.2014). In accordance with the Federal Law No. 61-FZ, the study did not require the approval of the Ethics Council of the Ministry of Health of the Russian Federation and permission from the Ministry of Health of Russia, as this study had an observational nature. The study was conducted in accordance with the legislative requirements and ethical principles set forth in the Federal Law "On the circulation of medicines" (No. 61-FZ of April 12, 2010, as amended), National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice," World Medical Association's Declaration of Helsinki (1964, with subsequent amendments), and the "Guidelines for Good Clinical Practice (ICH GCP)."

Study participants were randomized to two groups of 30 using the random number generator method. Patients in the treatment group received MPFF 1000 mg daily for 2 weeks before the scheduled sclerotherapy and for at least 2 months after the procedure. The control group underwent sclerotherapy without MPFF treatment. The first sclerotherapy session was performed 3-5 days after the last menses. Prior to injection of vein-sclerosing agent into the target intradermal vein, blood samples were obtained from the central vein of the target vascular cluster using Vacutainer® tubes (Becton, Dickinson

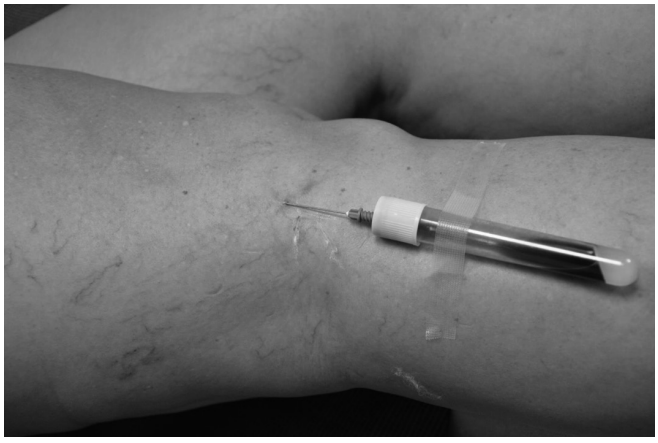

Figure 2.—Obtaining a blood sample from the central (feeder) vein.

and Company, Franklin Lakes, NJ, USA) to evaluate the levels of C-reactive protein within the high-sensitivity range (hs-CRP), histamine, interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and vascular endothelial growth factor (VEGF) (Figure 2). To measure the systemic inflammatory response, blood samples were obtained from the forearm vein in 15 patients from the control group.

Microsclerotherapy was performed according to standard protocols. To prevent the sclerosant from entering the central vein of the target vascular cluster, the latter was compressed using a cotton wool pad. With the patient lying in a horizontal position, 5.0 mL of 0.2% sodium tetradecyl sulphate (Fibrovein™, STD Pharmaceutical, Plough, UK) or 6.0 mL of 0.5% polidocanol (Aethoxysklerol®, Kreussler Pharma, Wiesbaden, Germany) were injected into the intradermal veins along the perimeter of the central vein using a 2-mL syringe and 30-G needle. Following the procedure, cotton wool pads were applied in the plane of the target vascular cluster, and class 2 RAL compression stockings put on. Day-time compression was prescribed for 10 days both in control and MPFF groups. During this time patients continued to take MPFF. No other systemic or local agents were administered in either group. Repeated blood samples were obtained from the central vein of the target vascular cluster on Day 10. The central (feeder) vein was obliterated with 0.5% STD or 0.75% POL. If required, microsclerotherapy for intradermal veins in other locations was undertaken. At each subsequent visit, photographs of the target vascular cluster were made

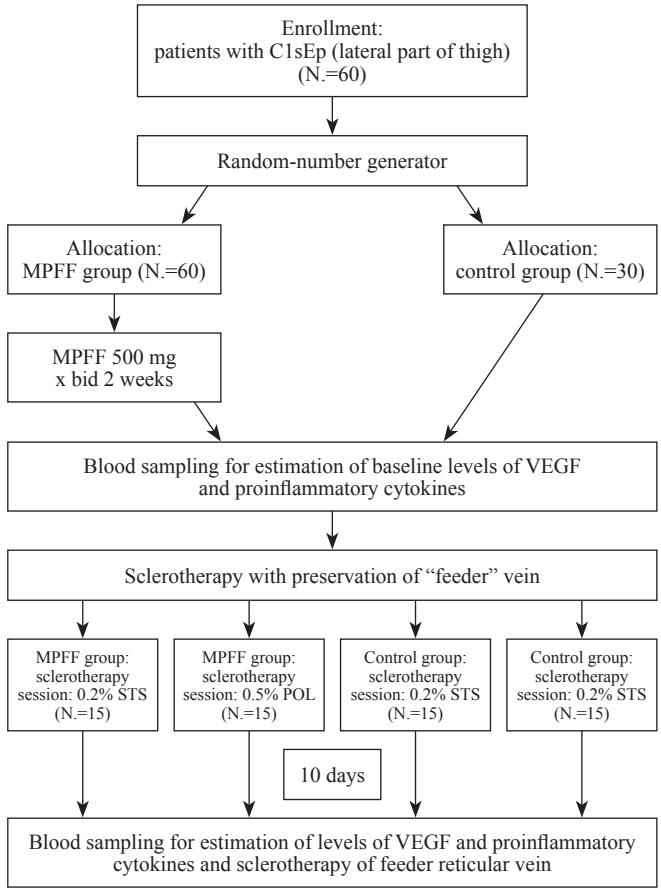

Figure 3.—CONSORT diagram showing trial enrolment, allocation, follow-up and analysis.

in order to assess long-term outcomes in both the MPFF and control groups. However, no additional injections of sclerosant were performed. The study design is presented in Figure 3.

Statistical analysis

Statistical analyses were conducted using the SPSS v. 17 software and included comparisons using the conventional non-parametrical tests.

Results

Patient age and BMI as well as baseline levels of blood inflammatory markers and markers of endothelial dysfunction were evenly matched between the MPFF and

TABLE I.—*Baseline levels of inflammatory markers and endothelial dysfunction in blood samples taken from the central vein of the target vascular cluster.*

Characteristics	MPFF (N.=30)	Control (N.=30)	P value
Age, years	30.4±3.8	31.2±4.1	NS
BMI, kg/m²	21.8±2.2	20.1±3.1	NS
Baseline levels			
VEGF, pg/mL	222.4±10.6	221.2±9.9	NS
TNF-α, pg/mL	5.4±0.9	5.2±1.3	NS
IL-1, pg/mL	4.8±0.7	4.6±1.2	NS
Histamine, µg/L	46.9±13.4	47.1±14.1	NS
hs-CRP, mg/L	1.5±0.5	1.1±0.9	NS

BMI: Body Mass Index; NS: not statistically significant.

control groups with no statistically significant difference (Table I). In blood samples obtained from the central vein of the target vascular cluster at Day 10 after microsclerotherapy, there was a statistically significant increase in all markers of endothelial dysfunction. In contrast, levels of markers in blood samples taken from the forearm veins before and after microsclerotherapy did not differ.

C-reactive protein

The increase in local CRP levels in response to injection of sclerosant is evidence of venous wall inflammation and is one of the treatment effects of sclerotherapy. In both groups, there was a significant local increase in CRP levels at Day 10 after microsclerotherapy (P<0.0001 in both groups). The increase in CRP levels was also significantly greater in the control group (8.3±1.0 mg/L) compared with the MPFF group (6.0±0.9 mg/L; P<0.001) (Figure 4), suggesting that MPFF treatment had reduced and localized the venous wall inflammation induced by administration of sclerosant.

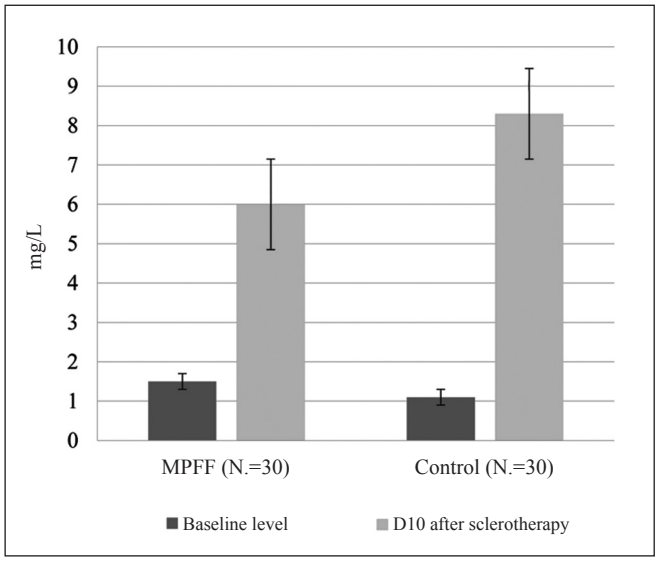

Figure 4.—High-sensitivity C-reactive protein (hs-CRP) levels.

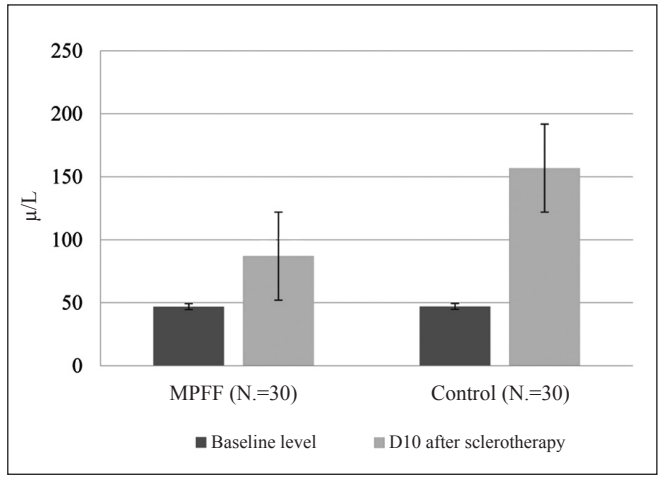

Figure 5.—Histamine levels.

Histamine

On Day 10 after sclerotherapy, histamine levels were significantly increased in both groups vs baseline values (P<0.0001 in both groups). However, these levels were significantly lower (almost twofold) in the MPFF group (87.0 ± 9.8 µg/L) comparing the control group (156.9±33.9 µg/L, P<0.001) (Figure 5).

Interleukin-1

Following sclerotherapy, IL-1 levels increased to 5.9±0.4 pg/mL in the MPFF group (insignificantly, P>0.01) and to 7.6±0.6 pg/mL in the control group (significantly, P<0.01) compared with the baseline levels. The IL-1 level was also significantly lower in the MPFF group comparing to the control group (P<0.0003) (Figure 6).

Tumor necrosis factor-alpha

TNF-α levels had increased at Day 10 after sclerotherapy to 5.9±0.9 pg/mL and 7.5±0.4 pg/mL in the MPFF and control groups, respectively (Figure 7);

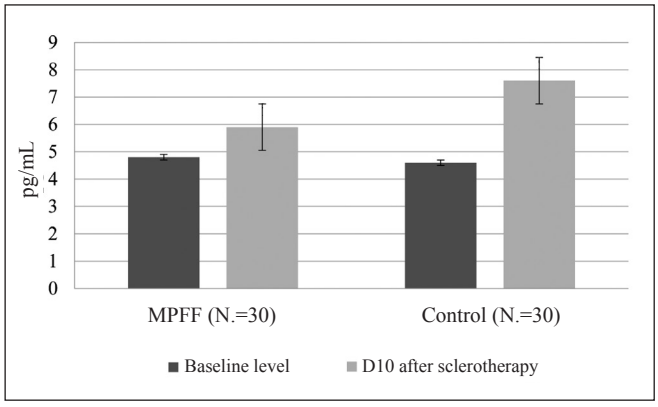

Figure 6.—Interleukin-1 (IL-1) levels.

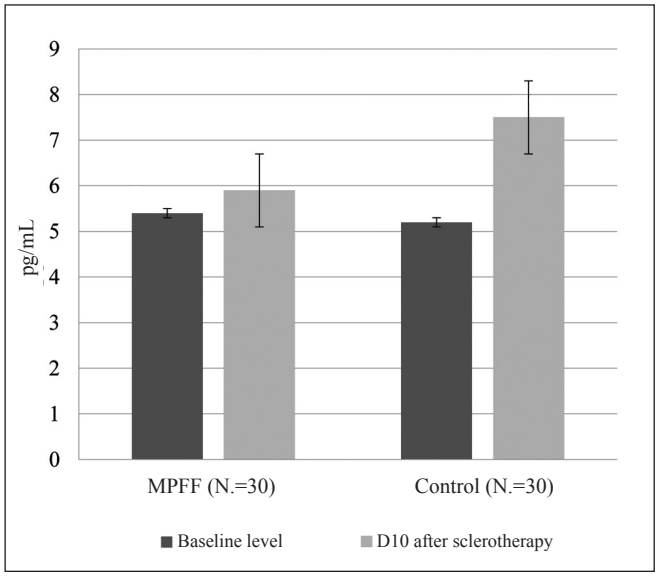

Figure 7.—Tumor necrosis factor-alpha (TNF-α) levels.

however, the increase was only statistically significant compared with baseline in the control group (P<0.001).

Vascular endothelial growth factor

VEGF levels were increased in response to sclerotherapy to 252.3±26.0 pg/mL and 325.1±47.7 pg/mL in the MPFF and control groups, respectively (Figure 8). However, the change in VEGF levels from baseline to Day 10 after sclerotherapy did not reach statistical significance in the MPFF group (P=0.5), whereas the increase was statistically significant in the control group (P<0.001).

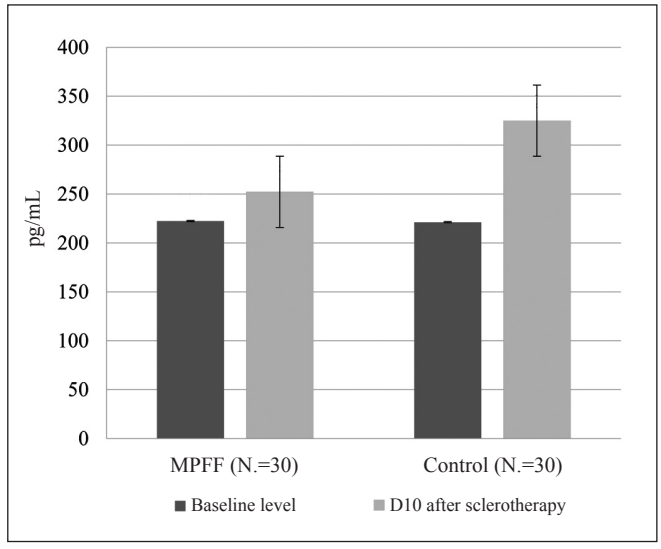

Figure 8.—Vascular endothelial growth factor levels.

Discussion

Microsclerotherapy with a low concentration of sclerosants is a very effective technique for the removal of reticular veins and telangiectasias, but is associated with a local vein-specific inflammatory response secondary to endothelial injury due to the expression of pro-inflammatory cytokines and growth factors. In the current study, baseline levels of markers of inflammation and endothelial dysfunction obtained from the central vein of the target vascular cluster showed no significant statistical difference between the MPFF and control groups and were within the normal range for those specific patients. When measured 10 days after sclerotherapy all markers had significantly increased from baseline levels in both groups. However, levels of inflammatory and endothelial dysfunction markers obtained from the control forearm blood were not modified after sclerotherapy, suggesting that the sclerotherapy technique had only induced a local inflammatory reaction.

Sclerotherapy triggers an acute-phase, non-specific response to tissue injury the first steps of which involve the release of inflammatory cytokines such as IL-1, IL-6 and TNF-α by cells at the injury site into the bloodstream. IL-1 has many important functions, including activation of lymphocytes and neutrophils, induction of chemotaxis of polymorphonuclear leukocytes and macrophages, and stimulation of endothelial cell pro-

liferation.[20] It is released during apoptosis of macrophages and is also produced by activated endothelial cells. TNF-α is produced by activated macrophages and duplicates the IL-1 action in many respects.[20] In particular, TNF-α activates leukocytes, and dramatically increases the formation of hydrogen peroxide and other free radicals by macrophages and neutrophils. High TNF-α levels have been linked to such negative effects of sclerotherapy as distant phlebitis and thrombophlebitis, as well as skin necrosis.[21] In the current study, expression of both IL-1 and TNF-α was increased after microsclerotherapy, but levels of both cytokines were significantly lower in the group that had received MPFF compared with the control group. Furthermore, in the MPFF group, the increased levels of TNF-α observed 10 days after sclerotherapy did not reach statistical significance compared with baseline. The inhibition of expression of certain interleukins is a feature of MPFF that has been proven *in-vitro* and animal studies.[22] However, this is the first time this has been described in clinical practice.

The release of pro-inflammatory cytokines such as IL-1, TNF-α, and, particularly, IL-6, mobilizes the body's immune reaction including the production of CRP by the liver. CRP is involved in the activation of the complement system, monocytes, and in the up-regulation of the expression of adhesion molecules ICAM-1, VCAM-1, and E-selectin on the endothelial surface. According to recent studies, local, low-level inflammation plays an important role in the pathological remodeling of the arterial wall, atherosclerosis progression, as well as the formation of varicose vein fibrosis.[23, 24] A slightly elevated baseline CRP level, which can be determined using highly sensitive assays, reflects inflammatory activity in the inner layers of arteries and veins. Consistently elevated levels of CRP are a predictor of arterial restenosis and occlusion, as well as recurrent venous thrombosis and thrombophlebitis. A normal CRP value is up to 1.0 mg/L. The increase in local CRP levels in response to injection of sclerosant is therefore evidence of venous wall inflammation and is one of the treatment effects of sclerotherapy. The severity and duration of the inflammatory response is dependent on the rate of adverse reactions, such as phlebitis and thrombophlebitis. In the current study, the local increase in CRP levels that occurred after microsclerotherapy was significantly less in patients that had received MPFF, suggesting that it was able to reduce the venous wall inflammation induced by administration of sclerosant.

Inflammatory cytokines also upregulate important mediators of angiogenesis and vascular permeability, such as histamine and VEGF. Histamine, is a tissue hormone and neurotransmitter that regulates vital body functions and plays an important role in inflammation and the pathogenesis of several diseases. It is stored in mast cells and basophils, where it is bound with protein and proteoglycan in a matrix of granules. Upon activation, basophil and mast cell degranulation releases histamine, and its content in blood and tissue fluid increases. Histamine liberators (releasing factors) are numerous and include detergent sclerosants. Sclerotherapy-induced histamine release, such as that seen in the current study, activates histamine H1 receptors on vascular cells, resulting in dilation of capillaries with an increase in their permeability, blood cell sludging, and swelling of perivascular tissues. MPFF is not known to have antihistamine activity, and so its beneficial effects on histamine levels are probably mediated by preventing the activation of endothelial cells and leukocytes.

VEGF is a glycoprotein that binds only to endothelial cells and stimulates their proliferation. In addition to its angiogenic action, VEGF significantly increases vascular permeability. Active synthesis of VEGF occurs in response to hypoxia, chemical, thermal or mechanical damage to the endothelium. During the early period after sclerotherapy, enhanced expression of VEGF stimulates angiogenesis with the formation of small red intradermal vessels (so called "matting"), and later can be a cause of the relapse of telangiectasias.[25-27] As expected levels of VEGF were increased in both groups following sclerotherapy; however, the increase compared with baseline only reached statistical significance in the control group.

The beneficial effects of MPFF on markers of inflammation and endothelial dysfunction suggest that there is considerable rationale for its use as a concomitant treatment in patients undergoing sclerotherapy to reduce a number of undesirable side effects of the procedure that negatively affect the cosmetic outcome and patients' quality of life. MPFF limits expression of pro-inflammatory markers of the acute-phase reaction and stimulation of CRP thereby reducing and localizing

the venous wall inflammation induced by administration of the sclerosant. The beneficial effects on levels of TNF-α suggest that administration of MPFF for the entire course of phlebosclerosis treatment may also protect against phlebitis, thrombophlebitis, and skin necrosis. By inhibiting VEGF-induced angiogenesis, MPFF may reduce vascular permeability and swelling of the perivascular tissues. MPFF has recently been shown to limit postsclerotherapy inflammation in the surrounding microvascular network in an animal model.[11]

In summary, microsclerotherapy for reticular veins and telangiectasias with the use of modern detergent sclerosants is associated with a local vein-specific inflammatory response due to expression of typical pro-inflammatory cytokines and growth factors. Prescription of MPFF for 2 weeks prior to phlebosclerosing treatment and throughout the postoperative period reduces the vein-specific pro-inflammatory response. The current study complements the results of previous work that examined the effects of MPFF in combination with sclerotherapy on the symptoms of telangiectasias.[28] In this trial, MPFF 2 tablets daily for 2 months, combined with a microsclerosing treatment, significantly relieved patients' symptoms and improved their quality of life. In addition, the frequency of side effects due to the procedure was very low (2.4%). MPFF has also been associated with improved treatment outcomes in the results of varicose vein procedures following administration in the perioperative period.[15, 16, 29]

Conclusions

Microsclerotherapy with the use of low-concentration detergent sclerosants is associated with a local vein-specific inflammatory response, as demonstrated by a significant increase in the levels of specific pro-inflammatory cytokines and growth factors at the site of intervention. The procedure is not associated with a systemic pro-inflammatory response, as levels of pro-inflammatory markers and markers of endothelial dysfunction in blood samples taken from the forearm vein remained normal. Prescription of MPFF at a standard dose of 1000 mg daily for 2 weeks before sclerotherapy and for the entire postprocedural period resulted in a significant reduction in the vein-specific inflammatory response, and can be expected to reduce the rate of sclerotherapy adverse effects.

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Conflicts of interest.—Vadim Y. Bogachev has received speaking fees from Servier. All other authors declare no conflict of interest.

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