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Клиническая эффективность биофлавоноидов в лечении вторичной лимфедемы нижних конечностей

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Цель. Изучение эффективности применения комбинации препарата микронизированной очищенной фракции флавоноидов (МОФФ) и эластической компрессии у пациентов с приобретенным лимфостазом.

Материалы и методы. В исследование были включены 60 пациентов с вторичной лимфедемой нижних конечностей II стадии по M. Foeldi. В результате рандомизации методом конвертов пациенты разделены на 2 группы. 1-ая группа (n = 30) — консервативное лечение (МОФФ, 1000 мг/сут) в сочетании с эластической компрессией (гольфы 3-го класса); 2-ая группа (n = 30) — только компрессионная терапия (гольфы 3 класса). Пациентам проводилось физикальное обследование, включающее измерение длины окружности конечности на разных уровнях.

Результаты. У пациентов 1-й группы длина окружности нижней трети голени через 1 мес. уменьшилась на 8,15% (p = 0,005), к концу лечения — на 10,6% (p < 0,001), средней трети голени — на 3,15% (p = 0,001) и 4,78% (p < 0,001), верхней трети голени — на 4,08% (p < 0,001) и 5,99% (p < 0,001) соответственно. К концу наблюдения (3 мес.) во 2-ой группе длина окружности голени в нижней трети (29,68 ± 4,67 см) была значимо больше в сравнении с 1-ой группой (26,65 ± 2,92 см, p = 0,035). Нежелательных реакций в группе МОФФ зарегистрировано не было.

Заключение. Применение комбинации МОФФ и эластической компрессии уменьшает объем нижних конечностей пациентов с приобретенной лимфедемой в большей степени, чем изолированное использование эластической компрессии. Положительное клиническое действие, отсутствие нежелательных реакций у пациентов, принимавших МОФФ, позволяют рекомендовать использование МОФФ в схемах фармакотерапии вторичной лимфедемы нижних конечностей.

Ключевые слова: *МОФФ; лимфедема; лимфостаз; слоновость; биофлавоноиды; венотоники; флебопротекторы*

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Clinical effectiveness of bioflavonoids in the treatment of secondary lower limb lymphedema

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AIM: This study aimed to investigate the effectiveness of the application of a combination of the preparation of micronized purified flavonoid fraction (MPFF) and elastic compression in patients with acquired lymphostasis.

MATERIALS AND METHODS: Sixty patients with stage II secondary lower limb lymphedema according to M. Foeldi were included. The patients were divided into two groups through randomization with the envelope method. The first group (n = 30) was subjected to a conservative treatment (MPFF, 1000 mg/day) coupled with elastic compression (3rd class compression stockings). The second group was given compressive therapy (third-class compression stockings). The patients were physically examined through the measurement of the circumference of the limb at different levels.

RESULTS: In the first group, the circumference of the lower third of the shin decreased by 8.15% ($p = 0.005$) after 1 month and by the end of treatment – by 10.6% ($p < 0.001$), of the middle third of shin – by 3.15% ($p = 0.001$) and 4.78% ($p < 0.001$), and of the upper third–by 4.08% ($p < 0.001$) and 5.99% ($p < 0.001$). By the end of the observation period (3 months), the circumference of the lower third of the shin in the second group (29.68 ± 4.67 cm) was significantly greater than that in the first group (26.65 ± 2.92 cm, $p = 0.035$). No adverse reactions were observed in the MPFF group.

CONCLUSIONS: The volume of the lower limbs of patients with acquired lymphedema decreased after using a combination of MPFF and elastic compression to a larger extent than after the isolated use of elastic compression. Patients taking MPFF had a positive clinical effect without adverse reactions. Therefore, MPFF could be used in the pharmacotherapy of secondary lymphedema of the lower limbs.

Keywords: *MOFF; lymphedema; lymphostasis; elephantiasis; bioflavonoids; venotonics; phleboprotectors*

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In the practical activity, a doctor often has to deal with edema syndrome. Chronic lower limb (LL) edema is often characterized by a debilitating condition and negatively influences the quality of patients' life [1,2]. One of the most common causes of this syndrome is chronic insufficiency of the lymphatic system [3]. Lymphedema is a chronic, polyetiological, slowly progressing disease caused by structural disorders in the lymphatic system and functional disorders in the endothelium [4,5]. In recent years, the incidence of lymphedema is seen to be on the rise.

A steadily progressive course of this disease requires life-long treatment [6,7]. Choosing an optimal treatment for LL lymphedema is not an easy task [4,8,9]. Despite the existing data on the effectiveness of surgical and conservative treatments for lymphedema, there still exists an opinion about the futility of treatment. As per leading scientific communities, systematic conservative methods play a major role in the treatment of lymphedema. The modern version of these methods includes a complex application of physiotherapy, podiatry, rehabilitation, and pharmacotherapy [10,11].

The application of pharmacotherapy includes functional optimization of the contractile apparatus of the lymphangion, regulation of the motor function of lymphatic vessels, prevention of erysipelas, and improvement in oxygenation of the tissues and rheological properties of blood [12,13]. Modern methods of treatment are multimodal; therefore, they are also aimed at reducing the edema and discomfort of the affected limb [14].

According to the position of the International Society of Lymphology, the role of bioflavonoids in the treatment of lymphedema is not defined [15]. Despite this, researchers continue to investigate the role of bioflavonoids in treating lymphedema of different etiologies. In clinical practice, bioflavonoids play a leading role in the pharmacotherapy of lymphedema and are the drug of choice in the treatment of patients with chronic venous diseases as they increase the venous tone, reduce vascular wall permeability, and improve the outflow of lymph [6,16,17].

Experimentally, it was shown that bioflavonoids stimulated the division of lymphatic endothelium by budding and formation of the lymphatic capillary network. As a result, the total absorption area of the lymphatic capillary networks and the volume of lymph reabsorption increased [18-20]. The most widely used bioflavonoid drug in clinical practice is the preparation of micronized purified flavonoid fraction (MPFF).

This study **aimed** to study the effectiveness of a combination of the preparation of MPFF and elastic compression in the treatment of patients with acquired lymphatic insufficiency.

MATERIALS AND METHODS

Research work was carried out at the Department of Cardiovascular, X-ray Endovascular, Operative Surgery, and Topographic Anatomy of Ryazan State Medical University in 2019–2020. The study was registered on the ClinicalTrials.gov platform (identifier NCT04360889) and was approved by the local ethics committee of Ryazan State Medical University (Protocol No. 2 of October 08, 2019).

Inclusion criteria: Patients with stages I–II secondary LL lymphedema according to M. Foeldi, aged 18–85 years, and those who gave written informed consent to participate in the study were included. To confirm the diagnosis, patients were subjected to a physical examination that included measuring the limb circumference at different levels, thorough history-taking, and an ultrasound scan of the soft tissues and veins of the LLs.

Exclusion criteria: Patients with chronic venous disease (varicose veins, post-thrombotic disease, phlebopathy, and angiodysplasia); significant arterial pathology; history of venous thromboembolic complications (deep vein thrombosis, superficial vein thrombophlebitis, and pulmonary thromboembolism); diabetes mellitus and its complications; infectious diseases within 3 months before screening for the study; and decompensated cardiac, renal, or pulmonary failure were excluded from the study.

The study included 60 patients aged 31–85 years with secondary LL lymphedema. Based on the randomization results by the envelope method, the patients were divided into two equal groups. During the observation period (3 months), patients in the first group received conservative treatment (MPFF, 1000 mg/day) and 3rd class elastic compression, while patients in the second group received only 3rd class compression therapy. The groups were comparable in gender, age (mean age of patients in group 1: 58.14 ± 2.05 years and in group 2: 60.10 ± 3.45 years), and frequency of concomitant pathology.

The clinical efficacy of treatment was assessed by the dynamics of the circumference of LLs at different levels. This noninvasive diagnostic method is used in clinical studies to determine the evidence of the process that caused derangement of lymph drainage in the limbs [3,21,22]. The method is not specific to the lymphatic system; however, it is necessarily used while choosing an appropriate treatment method and assessing its effectiveness. An inelastic tape measure with tape holding is used. There is a known variant for measuring the circumference of the limb at certain intervals, for example, 10 cm. Circumference of the limb was measured in centimeters and was taken in the morning, at the same time, throughout all patient visits [3,21,23,24].

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Statistical processing of the results was performed using Statistica 13.0 software (Stat Soft Inc., USA). Data distribution type was determined using Shapiro–Wilk statistics. All analyzed parameters demonstrated normal distribution. Differences between groups were evaluated using the Student t-test. The critical level of statistical significance of the difference between the compared parameters was considered to be $p < 0.05$.

RESULTS AND DISCUSSION

The patients in the first study group (n = 30) showed a tendency toward a significant reduction of the volume of the limb at all levels between 1 and 3 months of therapy as compared to the initial condition (Table 1). Thus, edema in the lower third of the shin decreased by 8.15% ($p = 0.005$) after 1 month of treatment and by 10.6% ($p < 0.001$) by the end of the observation period, edema in the middle third decreased by 3.15% ($p = 0.001$) and 4.78% ($p < 0.001$), and edema in the upper third decreased by 4.08% ($p < 0.001$) and 5.99% ($p < 0.001$), respectively.

By the end of the observation period (3 months), the circumference in the lower third of shin in the second group (29.68 ± 4.67 cm, Table 2) was significantly larger than that in the first group (26.65 ± 2.92 cm, $p = 0.035$). No adverse phenomena were recorded in both the study groups.

Table 1. Dynamics of the Affected Limb Circumference at Different Levels in Patients from the First Group

Shin level	Circumference (cm)			P_{V0-V1}	P_{V0-V2}
	Screening (V0), M ± m	After 1 month (V1), M ± m	After 3 months (V2), M ± m		
Lower 1/3	29.81 ± 4.83	27.38 ± 3.08	26.65 ± 2.92	0.005	< 0.001
Middle 1/3	43.72 ± 5.21	42.34 ± 4.96	41.63 ± 4.90	0.001	< 0.001
Upper 1/3	45.06 ± 5.13	43.22 ± 5.02	42.36 ± 4.67	< 0.001	< 0.001

Table 2. Dynamics of the Affected Limb Circumference at Different Levels in Patients from the Second Group

Shin level	Circumference (cm)			P_{V0-V1}	P_{V0-V2}
	Screening (V0), M ± m	After 1 month (V1), M ± m	After 3 months (V2), M ± m		
Lower 1/3	29.81 ± 4.83	27.38 ± 3.08	26.65 ± 2.92	0.005	< 0.001
Middle 1/3	43.72 ± 5.21	42.34 ± 4.96	41.63 ± 4.90	0.001	< 0.001
Upper 1/3	45.06 ± 5.13	43.22 ± 5.02	42.36 ± 4.67	< 0.001	< 0.001

Thus, this study demonstrated the advantage of complex pharmacotherapy (MPFF) and compression treatments over isolated compression therapy. The reduction of limb edema in patients with secondary lymphedema treated with bioflavonoids has also been demonstrated by other authors. So, in the work guided by O.V. Fionik (2007), regression of LL edema by an average of 8% from the initial edema was reported in patients with lymphedema after a month's use of diosmin [13]. In the work of S. Michelini, et al. (2019), the use of a combined preparation containing bioflavonoids led to the reduction of limb circumference by 4.2 cm after 6 months of treatment [25].

The results obtained also agree with experimental works. Bioflavonoids are reported to have *phleboprotective, antiedematous*, and *anti-inflammatory* effects *in vivo*. It has been experimentally proven that bioflavonoids accelerate lymph transport and inhibit leukocyte activity and synthesis of pro-inflammatory mediators. In a series of studies by J.R. Casley-Smith, et al. (1985, 1996) diosmin reduced hip edema in laboratory animals with LL lymphedema [26,27].

In addition, in a double-blind, placebo-controlled study (n = 94) of upper limb secondary lymphedema, the use of MPFF preparation demonstrated an increase in the rate of lymph flow, which illustrates its lymphokinetic activity [28].

CONCLUSION

A complex application of a preparation of micronized purified flavonoid fraction and elastic compression in patients with acquired lymphedema demonstrated a more evident anti-edema effect and reduced volume in the lower third of the shin compared to the isolated use of elastic compression.

The positive clinical effect of micronized purified flavonoid fraction from the first month of treatment and the absence of adverse reactions allows it to be recommended for pharmacotherapy of secondary lymphedema of the LLs.

ADDITIONALLY

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Participation of authors. *R.E. Kalinin, I.A. Suchkov* — concept and design of research, editing, *D.A. Maksaev* — collection and processing of material, statistical processing, text writing.

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