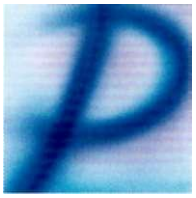

Changes in clinical manifestations and biophysical properties.of the great saphenous vein in transient premenstrual phlebopathy after 12 months' treatment with micronized purified flavonoid fraction

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Keywords:

venous insufficiency; phlebopathy; GSV; GSV reflux; menstrual cycle; premenstrua symptom; leg heaviness; transient premenstrual phlebopathy; MPFF

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Abstract

Aim. To study clinical manifestations and biophysical properties of the great saphenous vein (GSV) in 42 women with transient premenstrual phlebopathy (TPP) after 12 months of micronized purified flavonoid fraction (MPFF) treatment (1000 mg/day) and to compare GSV diameters measured in 84 legs before 10:00 and after 18:00. In 12 months the number of women with leg heaviness and swelling decreased to 2 (4.8%). The interphase gradient of the circumference (a difference between the circumferences during the secretory and menstrual phases) for the area over the ankle decreased from 6.87 mm to 3.0 mm. During the secretory phase GSV diameter decreased from 6.4 mm to 4.9 mm in the morning and from 72 mm to 5.3 mm in the evening. Interphase gradient of GSV diameter (a difference in diameters measured during the secretory and menstrual phases) decreased from 1.2 mm to 0.5 mm in the morning and from 1.1 mm to 0.5 mm in the evening. Only 2 patients out of 18 with an initial evening reflux of 11cm had an evening reflux of not more than 3.5cm. No patients had morning reflux.

Conclusion. Administration of MPFF (1000 mg/day) over 12 months, in the form of intermittent cyclic 15-day courses which started 15 days before menstruation, causes a decrease in leg swelling and elimination of premenstrual leg heaviness in 95.2% of women. It also provides the recovery of GSV diameter along the entire length and a total elimination of premenstrual morning reflux in the secretory phase.

Introduction

Nowadays, functional venous disorders are widespread.[1-3] Transient premenstrual phlebopathy (TPP) is considered to be a particular venous problem in fertile women. Its symptoms include leg heaviness, aching pain, leg swelling, and increased tiredness before menstruation that disappear at the beginning of the menstrual cycle. The reason for such a phenomenon is changes in biophysical properties of the venous wall. In TPP, as well as in transient orthodependent evening phlebopathy, venous tone decreases due to the increased creeping ability of the venous wall. To understand the processes that occur in the venous wall during prolonged orthostatic stress, it is useful to borrow the term "creep" from solid-state physics. In solid-state physics the creep of substances, or after effect, or slowly occurring deformation of a solid body, occurs under the influence of a constant load or stress over time. In settings of prolonged vertical load, it is this creep that can lead to a substantial dilation of the vein lumen.However, an additional clinically significant hormone-induced increase in the expansibility of the venous wall during the secretory phase of the menstrual cycle is thought to be a specific feature of TPP[4]

In some patients phase venous dilation may be to such an extent that it causes transient premenstrual great saphenous vein (GSV) reflux due to the relative insufficiency of the valves. By contrast with reflux in orthodependent evening phlebopathy, transient premenstrual GSV reflux is registered only during the secretory phase in the morning with minimal orthostatic loading.[4]

TPP treatment can be motivated by a monthly decrease in physical activity and quality of life.[5] Optimistic results of MPFF treatment in premenstrual syndrome[5] and a positive experience with MPFF administration in transient orthodependent evening phlebopathy[6] created a basis for studying clinical and biophysical peculiarities of MPFF treatment effect in TPR Such a therapy should take into the consideration the fact that a provoking factor - monthly changes in the endocrine profile which are natural in fertile women - cannot be excluded.

Intermittent cyclic 15-day courses of drug administration prescribed only for the second part of the menstrual cycle are considered to be a peculiarity of the proposed treatment protocol.

Aim: to study changes in clinical manifestations and biophysical properties of the great GSV in TPP of the lower-limbs with a 12-month MPFF treatment in a form of intermittent cyclic 15-day courses.

Material and methods

Clinical observation

From 2016 to 2019 a total of 42 women aged from 21 to 40 years (mean age 31.3 ± 8.9) were examined. At the beginning of the study all of them had leg heaviness and swelling which occurred before menstruation and disappeared in the first part of the menstrual cycle.

Inclusion criteria: parous women at their fertile age with a regular menstrual cycle during the last 6 months suffering from leg heaviness and swelling that occur before menstruation and disappears at the beginning of the menstrual cycle with usual daily activity; voluntary informed consent to participate in the study.

Exclusion criteria: regular leg heaviness and swelling which are not associated with the menstrual cycle; chronic venous disease (CVD) C2-C6 (according to the CEAP classification); history of venous thrombosis; lymphedema and lipedema; gynecological disorders; administration of combined oral contraceptive pills (COC); thrombophilia; chronic obstructive pulmonary disease (COPD); extra physical loading.

All women had had 1 to 3 uncomplicated natural births (1.72;95%CI:1.38-1.99). At the beginning of the study their mean body mass index was 25.15 ± 6.13kg/m^2. Their mean height was 164.5 ± 4.42. All patients lived in the city, had an office job, and did not go to fitness classes. All women had daily activity and a traditional night's rest.

Clinical assessment

During their menstrual cycle all women underwent a clinical and instrumental examination twice: at days 1 to 4 (menstrual phase), and 25 to 28 (secretory phase).[7] The intensity of leg heaviness was assessed according to VAS-10.

The circumference of the area over the ankle and of the muscular part of the calf (its upper third) was measured with a measuring tape. The measuring levels were marked on the skin with indelible ink. The measuring levels were also photographed. The previous study showed that in case of no lymphedema and inflammation the changing increase of the calf volume (first of all its muscular part) within 24 hours is mostly caused by regional venous hypervolemia.[8]

To evaluate the influence of estrogens and progesterone during the secretory phase of the menstrual cycle on changings of the limb circumference, the interphase gradient of the circumference (IGC) was calculated; this is a difference between the circumferences during the secretory and menstrual phases.[4]

Duplex ultrasound scanning

Duplex ultrasound scanning (DUS) of the veins was performed according to the international protocol.[9] After a traditional examination, morning and evening DUS results (obtained before 10:00 and after 18:00 during the menstrual (1 to 4 days) and secretory (25 to 28 days) phases were obtained, to study the reaction of the GSV to a prolonged orthostatic loading.[7]

According to the previous study, in TTP all trunk veins cyclically dilate during the secretory phase; however, this happens to a greater extent with the GSV.[4] Therefore, the present research is aimed at monitoring GSV. Its diameter was measured at 1 cm from the saphenofemoral junction (including the GSV reflux zone if any). To have an identical projection of the repeated scanning (in the morning and in the evening during the menstrual and secretory phases before during and after the treatment) in the case of complex leg geometry, the sensor was put in the area with a minimal distance from the skin to the vein in the proximal part of the reflux. This area was marked on the skin with indelible ink and then photographed as well.

The diameters of veins were measured by the same physician with the patient in the upright position with normal breathing, at room temperature.

To identify the pathophysiological GSV features, two calculated values were used. The first constituted the difference in vein diameters measured during the secretory and menstrual phases (interphase gradient of the diameter-IGD). This value allowed assessment of hormonal effects on the vein. The second was the difference in vein diameters measured in the morning and in the evening during the secretory and menstrual phases (orthostatic gradient of "evening-morning" diameter-OGD "evening-morning"). This value aided understanding of the GSV reaction to long orthostatic loading.[10]

These values integrally characterize the biophysical properties of the vein. The first evaluates the change in the expansibility under the hormonal influence during the secretory phase. The second demonstrates the degree of the creeping ability of the vein, being the value of its gradual expansion at long vertical loading.[4]

GSV reflux was defined as retrograde flow of >0.5 sec. duration[9,11] after a Valsalva maneuver and manual compression and decompression of the distal limb.

Considering the fact that the lesion at phlebopathy is usually of a bilateral nature, the study included GSVs in 84 legs.

Treatment

All patients had a 12-month MPFF monotherapy in the form of intermittent cyclic 15-day courses which started 15 days before menstruation. The dose of the drug was 1000 mg once a day.

The effectiveness of this protocol was assessed by comparing the results of the examination performed before and after the 3rd and the 12th month of treatment.

The assessment of quality of life during the secretory phase was done according to the CIVIQ-2 basing on pain and physical, social, and psychological factors.[12]

The safety and tolerability of the drug was studied with active identification of possible digestive complaints, and allergic and other manifestations, as well as general tolerability and significant laboratory safety tests (hematology, medical biochemistry, urinalysis).

The statistical analysis was performed using the nonparametric Wilcoxon test. The value $P<0.5$ was considered statistically significant. The mean values were determined with the 95%CI.

Results

In 3 months the number of women with leg heaviness during the secretory phase decreased from 42(100%) to 4(9.5%). The intensity of leg heaviness in those women who still had it also decreased from 5.2(95%DI:4.7-5.7) to 0.3 (95%DI:0.0-0.6) ($P<0.0001$) according to VAS-10 scale. In 12 months the number of women with such a complaint decreased to 2(4.8%), and the intensity in those who still felt heavy legs decreased to 0.1(95%DI:0.0-0.2) ($P<0.0001$) according to VAS-10 scale.

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of a 12-month treatment with MPFF were not surprising. With MPFF treatment, venous tone was increased due to the modulation of noradrenergic signaling through the reduced norepinephrine metabolism.[14,15]

The treatment method proposed in the study differs from a traditional prescription of the drug due to its intermittent cyclic courses connected with the period of maximum progesterone aggression. Such a theoretical background and the chosen treatment guidelines seem to be correct, given that the examined women experienced both subjective and objective improvements.

Administration of MPFF (1000 mg/day) over 12 months in the form of intermittent cyclic 15-day courses in the second part of the menstrual cycle was proven to be safe and well-tolerated.

Conclusion

Detailed analysis of biophysical processes in veins at TPP during the menstrual cycle allowed a change in the prescription methods for phlebotropic drugs.

Administration of MPFF (1000 mg/day) over 12 months in the form of intermittent cyclic 15-day courses starting 15 days before menstruation brings about a significant decrease of leg swelling and elimination of premenstrual leg heaviness in 95.2% of women suffering from TPP, and improves patient's quality of life.

The proposed treatment over 12 months also provides the recovery of GSV diameter along its entire length in menstrual and secretory phases, and a total elimination of a transient premenstrual morning reflux in secretory phase due to a reduction of hormone-induced expansibility of veins

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