A topical combination of blackberry, *Centella asiatica*, sodium hyaluronate, vitamin E and Melilotus to relieve legs symptoms of venous insufficiency

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Abstract

Chronic Venous Insufficiency (CVI) is a clinical condition characterized by several legs symptoms: telangiectasias, reticular veins, varicose veins, edema, pigmentation, eczema, lipodermatosclerosis, white atrophy and ulcers. These symptoms are often associated with tired and heavy legs, leg pain, itching, legs and ankles swelling. This report analyzes the usefulness of a cream based on blackberry, *Centella asiatica*, sodium hyaluronate, vitamin E and Melilotus (Flavofort 1500® legs cream) to relieve leg symptoms in CVI. A group of 35 subjects (7 men and 28 women) with legs symptoms applied Flavofort 1500® legs cream on the legs, twice a day for 10 days. The symptoms were evaluated with a patient questionnaire at 4 steps: T0 (before cream application), T1 (just after first application), T2 (5 days after first application) and T3 (10 days after first application). A reduction of subjects (%) with legs symptoms was observed both after 5 day and after 10 days.

Materials and Methods

We evaluated Flavofort 1500® legs cream (Blackberry, Centella asiatica, Sodium Hyaluronate and Melilotus) in patients with legs symptoms, analyzing the reduction of symptoms and the patient opinion. Patients (n=35) with a diagnosis of venous insufficiency of different degree [from C0s to C4a according to Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification; not detected data] with bilateral leg symptoms (tired and heavy legs/leg pain/itching and tingling/varicose veins/ankles swelling/telangiectasias or reticular veins/ankles pigmentation/varicose veins) and no comorbidities were enrolled.

All patients underwent ultrasound examinations, of both legs, to assess superficial and deep veins of the lower limbs. This exam was performed using multi-frequency 7.5–10 MHz Doppler ultrasound probes (Sonos 1500B; Hewlett Packard, Palo Alto, CA). The room temperature was maintained between 18°C and 22°C.

In detail 7 men and 28 women were recruited. Their baseline characteristics are reported in the Table 1. The 14% of patients were aged between 26 and 35 years old, the 34% were aged between 36 and 50 years old and the 52% were over 50 years old.

Informed consent was obtained from all individual participants included in this analysis. All patients applied Flavofort 1500® legs cream (3 mL for each application; corresponding to the size of a nut) for 5 minutes of a gentle superficial massage in circulatory motion on the affected area (both calves and ankles), twice a day for 10 days. Patients were evaluated at 4 steps: T0 (baseline), T1 (just after first application), T2 (5 days after first application) and T3 (10 days after first application). At each step an evaluation of symptoms was conducted, while at the beginning and at the end of local treatment a patient judgment on skin characteristics (hydrated, bright, elastic, soft or velvety) was recorded. All patients filled in an assessment questionnaire at each step, assigning a score from 0 to 4 to the symptoms based on the severity of the symptom (score: 1=at all; 2=a little; 3=enough; 4=very much).

Results

The % of patients with legs symptoms (tired and heavy legs/leg pain/itching/cramps/legs and ankles swelling/telangiectasias or reticular veins/ankles pigmentation/varicose veins) decreases after 5 days of cream application and further after 10 days of cream application (Table 2, Figures 1 and 2).

Data showed that Flavofort 1500® , after 10 days of cream application, decreases the % of patients with: tired and heavy legs [–85%; P<0.05], leg pain [–67%; P<0.05], itching and tingling [–85%; P<0.05], cramps [–78%; P<0.05] (Table 2 and Figure 1), legs and ankles swelling [–82%; P<0.05], telangiectasias and reticular

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Key words: *Centella asiatica*; *Vaccinium myrtillus*; *Melilotus officinalis*; vitamin E; hyaluronic acid.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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veins [–91%; P<0.05], ankles pigmentation (redness and dark spots) [–87%; P<0.05], visibility and perceptibility of varicose veins (Table 2 and Figure 2) [–100%; P<0.05] (Table 2 and Figure 2). The data shown are related to the patients who assigned a score 4 to their symptoms, based on the severity of the symptom.

Most patients expressed a positive judgment on the pleasantness of the cream. After the treatment, the skin was smooth, soft, bright and hydrated.

Conclusions

The observations in this study show that Flavofort 1500® legs cream application can produce local benefits. The beneficial effects of local treatment with Flavofort cream may be seen by symptomatic evaluation of patients.

These findings, as preliminary data, suggest the usefulness of a formulation based on the association of Blackberry, Centella asiatica, Sodium Hyaluronate, Vitamin E and Melilotus to relieve legs symptoms of venous insufficiency. The association of a cream formulated by combining these substances with other phlebotonic agents opens a window of opportunities to be evaluated in more prolonged and larger studies.

Table 1. Baseline characteristics (T0).

| Patients (N=35) |                  |
|-----------------|------------------|
| Sex             |                  |
| Males           | 7 (20)           |
| Females         | 28 (80)          |
| Age distribution, N (%) |                  |
| 26-35 years     | 5 (14%)          |
| 36-50 years     | 12 (34%)         |
| >50 years       | 18 (52%)         |
| BMI             | 21-27            |
| Legs symptoms   |                  |
| Tired and heavy legs | 7 (20%)       |
| Leg pain        | 3 (9%)           |
| Itching and tingling | 7 (20%)     |
| Cramps          | 5 (14%)          |
| Legs and ankles swelling | 12 (34%) |
| Telangiectasias and reticular veins | 12 (34%) |
| Ankle pigmentation | 8 (23%)       |
| Varicose veins  | 8 (23%)          |

Table 2. Number and Percentage of patients with legs symptoms after: the first application (T1), 5 days of application (T2) and 10 day of application (T3) of Flavofort 1500® legs cream.

| Symptoms                                      | N (%) patients at T1 | N (%) patients at T2 | N (%) patients at T3 |
|------------------------------------------------|-----------------------|-----------------------|-----------------------|
| Tired and heavy legs                          | 4 (11)                | 2 (6)                 | 1 (3)                 |
| Leg pain                                      | 3 (9)                 | 2 (6)                 | 1 (3)                 |
| Itching and tingling                          | 7 (20)                | 4 (11)                | 1 (3)                 |
| Cramps                                        | 4 (11)                | 1 (3)                 | 1 (3)                 |
| Legs and ankles swelling                      | 10 (29)               | 5 (14)                | 2 (6)                 |
| Telangiectasias and reticular veins           | 5 (14)                | 2 (6)                 | 1 (3)                 |
| Ankle pigmentation (redness and dark spots)   | 7 (20)                | 3 (9)                 | 1 (3)                 |
| Varicose veins (visibility)                   | 2 (6)                 | 0 (0)                 | 0 (0)                 |
References

1. Lichota A, Gwoздzinski L, Gwoздzinski K. Therapeutic potential of natural compounds in inflammation and chronic venous insufficiency. Eur J Med Chem 2019;176:68-91.
2. Chong NJ, Aziz Z. A Systematic Review of the Efficacy of Centella asiatica for Improvement of the Signs and Symptoms of Chronic Venous Insufficiency. Evid-Based Complement Altern Med 2013;2013:627182:1-10.
3. Ulbricht C, Ethan B, Samuel B, et al. An Evidence-Based Systematic Review of Bilberry (Vaccinium myrtillus) by the Natural Standard Research Collaboration. J Diet Suppl 2009;6:162-200.
4. Available from: https://www.ema.europa.eu/en/documents/herbal-report/draft-assessment-report-melilotus-officinalis-l-lam-herba_en.pdf
5. Farbiszewski R, Glowinski J, Makarewicz-Plonska M, et al. Oxygen-Derived Free Radicals as Mediators of Varicose Vein Wall Damage. Vasc Endovasc Surg 1996;30:47-52.
6. Iannitti T, Rottigni V, Torricelli F, et al. Combination Therapy of Hyaluronic Acid Mesotherapeutic Injections and Sclerotherapy for Treatment of Lower Leg Telangiectasia Without Major Venous Insufficiency: A Preliminary Clinical Study. Clinical and Applied Thrombosis/Hemostasis 2014;20:326-30.

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