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The Efficiency of Magnesium Supplements for the Symptomatic Relief of Patients with Superficial Venous Reflux Disease

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Abstract

Objectives: Patients with superficial venous reflux disease admit to the outpatient clinics with a wide range of symptoms. Although none of the marketed medications disappear the varicosities, they are helpful to relieve the symptoms of the patients to a certain degree. We investigated the influence of the addition of magnesium oxide (MO) to the standard symptomatic treatment of patients with superficial venous reflux disease.

Materials and Methods: Thirty-two consecutive patients who were diagnosed with chronic superficial venous reflux disease were randomly divided into 2 groups. The first group (n=16) was treated with a Horse chestnut seed extract

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(HCSE)-calcium dobesilate combined therapy, whereas the second group was treated with HCSE-calcium dobesilate combined plus MO therapy.

Results: The scores of symptoms including mean burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and visual analog scale improved significantly in the second group with additional MO uptake at the end of the 2-week treatment period ($p<0.05$).

Conclusion: The addition of MO into the symptomatic treatment regime of patients is associated with a more efficient relief in symptoms and associated with a significant decrease in edema when combined with other anti-varicose vein agents.

Keywords: Superficial venous reflux disease, visual analog scale, magnesium, horse chestnut seed extract, calcium dobesilate

Introduction

Lower extremity venous insufficiency is a well-known, common health issue in the human population. Historically, it was described in ancient texts in China and Egypt. Pathology may be encountered among all age groups in the community worldwide, with a prevalence estimated between 30-40% in the general population[1-3]. The data regarding the incidence of varicose veins are indefinite; however, approximately 50% of people over 40 years are estimated to have varicose veins or telangiectasias in America and Europe[4]. Chronic venous insufficiency (CVI) is one of the most common causes of lower extremity discomfort, cramps, pain, edema, discoloration, and ulcer formation[4,5]. It is an important clinical condition leading to epidemiologic and socioeconomic consequences affecting the quality of life of patients. Increased incidence, diagnosis, and treatment costs result in a serious burden on the economy through medical costs and loss of work and attenuated quality of life[6,7].

The most common clinical findings related to long-standing venous insufficiency are telangiectasis, reticular, and/or varicose veins, whereas common symptoms are pain, cramping, itching, and complications related to venous ulcers, which are secondary to increased venous pressure due to valve insufficiency or venous obstruction[5]. Various treatment alternatives have been described for treating CVI as well as for the symptomatic relief of the affected patients. They include interventional and supportive methods. Compression stockings and medical therapy are supportive measures for pathology. The stockings act against the hydrostatic pressure of venous hypertension. Venoactive drugs relieve these symptoms by improving venous tone and capillary permeability[7].

Venoactive agents are the mainstay of standard symptomatic therapy in patients with venous reflux disease in addition to compression stockings which may be combined with various herbal and/or ionic mineral compounds. Among these, horse chestnut seed extract (HCSE) is a herbal agent frequently added to the regime of patients with venous disorders[8]. On the other hand, magnesium (Mg), which is an essential mineral for the body, has been suggested to improve vascular function[9] as well as act in the modulation of pain[10]; both of which are among the components of CVI.

In this research, we sought to investigate the efficiency of oral Mg supplements for the relief of symptoms in patients with chronic superficial venous reflux disease.

Materials and Methods

We included 32 consecutive patients who were diagnosed with chronic superficial venous reflux disease and were not amended for interventional treatment between November 11 and December 31, 2022, in this prospective study. All the patients were informed about

the study protocol in detail and researched following their consent. The study was approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee on November 10, 2022, with a decision number: 948.

The patients were randomly divided into two groups. Randomization was performed according to http://www.tufts.edu/~gdallal/PLAN.HTM, which revealed a sequence of 0100001100111001 and 0101010010101111, where 0 stands for allocation in Groups 1 and 1 in Group 2. The patients in Group 1 (n=16) received dobesilate calcium (Doxium 500 mg, twice daily) and HCSE (Venotrex Retard 50 mg, twice daily), and in Group 2 (n=16), patients were prescribed magnesium oxide (MO) (Magnorm 365 mg, once daily, before bedtime) in addition to the medications in Group 1. Age, gender, weight, symptoms, occupation, duration of staying still, and performance of any kind of sport were recorded. The diagnosis of superficial venous reflux disease was made by visual examination of the legs of the patients and confirmed with Doppler ultrasonography. Superficial venous reflux disease was categorized according to the 2020 updated version of the CEAP classification that stands for Clinical (C), Etiological (E), Anatomical (A), and Pathophysiological (P)[11].

The questioned symptoms were burning and heavy sensations in the legs, restless legs, cramps, and edema. Each symptom was graded between 0-10. All the patients were requested to fill out the visual analog scale (VAS). Patients were instructed regular medication use for a period of 2 weeks and re-investigated regarding the alteration of questioned symptoms at the outpatient clinic at the end of the study period. None of the patients used compression stockings on an outpatient clinic admission and were not prescribed compression stockings, at least during the research. Improvement in symptoms in Group 1 and Group 2, as well as the efficiency of the addition of MO preparation to the treatment, were analyzed and compared.

Patients with deep or superficial venous thrombosis or insufficiency, systemic or peripheric arterial diseases, immobile and seriously movement compromised patients, pregnant patients, patients who received surgical or interventional treatment against superficial venous reflux disease, or patients with short life expectancy, use of anticoagulants, pain killers, or any kind of any other medications, and patients who could not tolerate any agent prescribed against symptoms of superficial venous reflux were excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc., Chicago, Illinois, USA) 16.00 Inc.. Continuous variables are presented as mean ± standard deviation (mean ± SD). Categorical variables are given as number and percentages. The distribution of the data was analyzed by the Kolmogorov-Smirnov test. Normally, distributed continuous variables were analyzed with Paired-Samples t-test. Continuous values without a normal distribution were analyzed with the Wilcoxon-Signed rank test. Proportional analysis and changes in parameters at different time intervals were evaluated using the chi-square test and Fisher's exact test. Pearson correlation was used for the analysis of the correlation between the variables. Statistical significance was defined as $p<0.05$.

Results

There were 16 patients in each group. The mean age of the patients was 46.1±15.9 in Group 1 and 53±11.7 in Group 2. Female/male ratio in Group 1 was 3 whereas, in Group 2, there were 12 females and 4 males. Patients seldomly performed routine sports activities in both groups. Mean scores for each symptom i.e. burning and heavy sensations on legs, restless legs, cramps, and edema, and VAS scores of the patients in both groups as well as the demographic features of the patients, are presented in Table 1. Except for the burning sensation in the legs (Group 1: 5.06±1.81 vs. Group 2: 2.44±1.78, p=0.02), none of the other symptoms and VAS scores differed significantly between both groups.

Mean scores for burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and VAS scores on admission were 5.06±1.81, 3.38±3.07, 7.31±1.88, 1.88±2.65, 7.13±2.15, and 6.81±0.98 respectively in Group 1. The values at the end of 2-week treatment period changed to 2.44±1.98 for burning sensation, 1.31±1.91 for heaviness, 3.56±2.22 for cramps, 0.56±1.24 for edema, 3.18±2.11 for restless leg and, and 3.43±2.89 for VAS score. Except for the edema symptom (p=0.06), all the other symptoms in patients improved significantly in patients (Table 1).

In Group 2, mean burning sensation, heaviness, cramps, edema, restlessness on the affected leg, and VAS scores on admission were 6.52±2.18, 4.05±3.17, 7.23±1.85, 2.47±2.85, 6.88±2.05, and 6.82±1.07, respectively. The symptom scores of the patients improved significantly in Group 2 at the end of the 2-week treatment period (1.76±1.85 for burning sensation, 1.47±2.25 for heaviness, 1.23±1.52 for cramps, 1.05±1.47 for edema, 2.47±2.18 for restless leg and 5.05±0.82 for VAS score) including edema (pre-treatment edema score: 2.47±2.85, post-treatment edema score: 1.05±1.47, p=0.03) (Table 2).

The improvement in symptoms in both groups was also compared at the end of the study period. There were no statistically significant differences between burning sensation (Group 1: 2.44±1.98 vs. Group 2: 1.76±1.85, p=0.16), heaviness (Group 1: 1.47±2.25 vs. Group 2: 1.31±1.91 p=0.45), edema (Group 1: 1.05±1.47 vs. Group 2: 0.56±1.24, p=0.27), restlessness (Group 1: 2.47±2.18 vs. Group 2: 3.18±2.11 p=0.17) on the affected leg and VAS scores (Group 1: 5.05±0.82 vs. Group 2: 3.43±2.89, p=0.24); however, patients in Group 2 exhibited significant improvement in cramps (Group 1: 1.23±1.52 vs. Group 2: 3.56±2.22, p=0.0007) with the addition of MO to the treatment regime (Tables 1, 2).

Discussion

CVI is a condition in which the valves in the veins of the legs malfunction, causing blood to flow backward and pool in the legs. The symptoms of CVI may include aching, heaviness, fatigue, itching, burning, and cramping in the legs, as well as visible varicose veins and skin changes such as eczema and pigmentation. Long-term complications of CVI can include skin damage, ulceration, and blood clots[12].

Table 1. Pre- and post-treatment scores of superficial venous reflux disease symptoms for Group 1

Group 1	Pre-treatment	Post-treatment	p-value
Burning sensation	5.06±1.81	2.44±1.98	**<0.01**
Heaviness	3.38±3.07	1.31±1.91	**<0.01**
Cramps	7.31±1.88	3.56±2.22	**<0.001**
Edema	1.88±2.65	0.56±1.24	0.06
Restlessness	7.13±2.15	3.18±2.11	**<0.001**
VAS scores	6.81±0.98	3.43±2.89	**<0.001**

VAS: Visual analog scale

Table 2. Pre- and post-treatment scores of superficial venous reflux disease symptoms for Group 2

Group 2	Pre-treatment	Post-treatment	p-value
Burning sensation	6.52±2.18	1.76±1.85	**<0.01**
Heaviness	4.05±3.17	1.47±2.25	**<0.05**
Cramps	7.23±1.85	1.23±1.52	**<0.01**
Edema	2.47±2.85	1.05±1.47	**<0.05**
Restlessness	6.88±2.05	2.47±2.18	**<0.01**
VAS scores	6.82±1.07	5.05±0.82	**<0.01**

VAS: Visual analog scale

The most common cause of CVI in the lower extremities is venous wall weakening, which also contributes to concurrent valvular insufficiency and alterations in venous hemodynamics. Increased hydrostatic pressure, venous stasis, and dilatation are the characteristics of these alterations. Consequently, both directly and indirectly, the microcirculation is disturbed, resulting in diffuse edema, pain, night/day (or both day and night) cramps, paresthesia, or restless legs syndrome of the legs[13].

One of the CVI treatment elements, Calcium dobesilate (2,5-dihydroxy-benzenesulfonate) (CD), is an angioprotective drug that mitigates the platelet activity, blood viscosity, and vascular permeability, as well as alleviates microcirculation and hemorheological anomalies owing to its vasoprotective and antithrombotic properties to treat both CVI and diabetic retinopathy[14,15]. Supporting these findings, the CD is reported to reduce erythrocyte aggregation and suspension viscosity[16] and inhibits thrombus formation and platelet aggregation in vascular grafts[17], antagonizing the release of thrombin- and collagen-induced serotonin from platelets, which clarifies its effect on reducing capillary permeability[18].

However, the results of human studies on CD, however, have been inconsistent. Some trials involving over 600 patients found it to be effective in reducing lower leg pain and decreasing the size of lower limbs after 7-12 weeks of treatment, but other research found no overall benefits for lower limb pain[19-21]. In a randomized, double-blind, placebo-controlled clinical trial, the CD was shown to improve the lymph physiology and symptoms of patients with CVI[20]. The varying results and subjectivity of pain assessments may be due to the drug being more effective in more severe cases of the condition.

Escin is the active ingredient of HCSE, which is used for treating conditions such as hemorrhoids, venous insufficiency, hematomas, and venous congestion[22]. Clinical studies of the vascular activity of β-escin have shown improved microcirculation, increased venous tone, decreased vascular permeability, and venous return leading to reduced edema[23]. Several studies have shown that taking oral HCSE can lead to a statistically significant improvement in leg pain and swelling compared with a placebo or baseline[23-27]. Taking 300 milligrams of HCSE twice a day for 12 weeks has been found to be as effective as compression therapy in reducing swelling and can be recommended for patients who cannot use compression therapy[27]. It is still uncertain whether HCSE treats CVI compared to placebo since the quality of the evidence is very low. In other words, HCSE treatments do not address underlying venous reflux; rather, they merely address some of the symptoms and manifestations of varicose veins. As a result, they work similarly to compression in that they temporarily relieve pain but do not perform any therapeutic functions[28].

Mg, which is the fourth-most abundant mineral in the body and second-most abundant intracellular cation, modulates endothelial function and vascular smooth muscle tone through participation in vascular calcification, thrombosis, and atherogenesis, the migration, and proliferation of vascular smooth muscle and endothelial cells[29,30]. According to observational prospective studies, both dietary[31,32] and serum Mg levels[9] are inversely related to cardiovascular disease risk. Even though experimental and epidemiological evidence suggests that Mg may be a beneficial therapeutic substance for mitigating cardiovascular risk[33], no interventional research has been conducted to examine how Mg supplementation affects cardiovascular events.

The results of our study indicate MO -attenuated edema in patients with superficial venous reflux disease. Literature includes reports indicating such potential of the agent, especially for cerebral edema, by decreasing the permeability of the blood brain barrier and being useful in patients with headaches[34]. In addition, Orlova et al.[35] revealed that hypomagnesemia was significantly associated with edema in pregnant women. However, such issues regarding Mg supplements is rather neglected.

In this study, we found that additional MO uptake in the symptomatic treatment regime of the patient favored a more efficient relief of symptoms as well as decreased

edema when combined with other anti-varicose vein agents. Even using HCSE-CD combined therapy as the first -line pharmacological treatment is not validated, additional MO support in the treatment was superior to this standard treatment itself, at least in the relief of pain.

Study Limitations

There are 2 major limitations of the study. First cohort size is rather small, comprising 32 patients in totaland 16 patients in each group. The second limitation regards to the duration of the treatment, which was 2 weeks. However, despite a limited number of patients and a short study period, the results were found promising. Further multi-center studies with a longer duration of follow up are warranted.

Conclusion

In conclusion, the results of the current study with a modest number of study cohorts indicated that the addition of MO to the anti-symptomatic treatment of patients with superficial venous reflux disease not only helped in better improvement of subjective symptoms but also relief of edema.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul Medipol University Non-Invasive Clinical Research Ethics Committee on November 10, 2022, with a decision number: 948.

Informed Consent: All the patients were informed about the study protocol in detail and researched following their consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Öztaş DM, Bıçakhan B, Erdinç İ, Uğurlucan M, Concept: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Design: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Data Collection and/or Processing: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Analysis and/or Interpretation: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Literature Search: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M, Writing: Önal B, Öztaş DM, Bıçakhan B, Hakgör A, Erdinç İ, Yıldız Y, Uğurlucan M.

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