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Randomized, Double Blind, Placebo-Controlled Clinical Trial to Evaluate the Lymphagogue Effect and Clinical Efficacy of Calcium Dobesilate in Chronic Venous Disease

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The aims of the present study were to investigate the effect of calcium dobesilate on lymph flow and lymphovenous edema in patients with chronic venous disease. It was a randomized, placebo-controlled, double-blind clinical trial. Patients received 1 capsule of 500 mg calcium dobesilate every 8 hours (1.5 g/day) or placebo by 49 days. By the end of the treatment period, only the patients treated with calcium dobesilate had normalization of lymphogammagraphy (capture index and speed of lymph flow; 80 and 78%, respectively). Only patients treated with calcium dobesilate had statistically significant reduction in the perimeter of leg, calf, and ankle. Twenty-two out of 25 (88%) calcium dobesilate–treated patients presented clinical improvement versus 5 out of 24 (20.8%) in the placebo group. One patient on calcium dobesilate developed rash and one patient on placebo complained of vomiting. In the present study, calcium dobesilate normalized lymph physiology and improved symptoms in patients with chronic venous disease.

Keywords: chronic venous disease; calcium dobesilate; lymph; edema; lymphogammagraphy

Chronic venous disease (CVD) is a common but underestimated disease.[1] A recent review of the literature in the English language found that prevalence of chronic venous insufficiency (CVI) varied from <1% to 40% in women and from <1% to 17% in men. Prevalence of varicose veins was higher, <1% to 73% in women and 2% to 56% in men.[2] The Framingham study showed a CVI annual incidence of 2.6% in women and 1.9% in men.[3]

Risk factors for CVI included older age, female sex, pregnancy, family history of venous disease, obesity, and occupations associated with orthostasis. Other factors, such as diet, physical activity, and use of exogenous hormone, were not completely documented.[2]

It has been estimated that the annual cost of venous ulcers is about $1 billion in USA.[4] The total cost of CVI to society (including direct and indirect costs) has been estimated to be $1 billion (US dollars) in countries like Germany, France, and UK.[1]

In Europe and Latin America, the use of venoactive drugs, also known as phlebotonics, venotonics, phlebotropics, and venotropics, in the treatment of CVI is common.[1,5] But the use of these medications is sometimes controversial.[6]

Calcium dobesilate is a synthetic venoactive drug acting on several levels (for review see Garay et al, 2005).[7] Among others, it inhibits capillary permeability induced by serotonin, bradykinin, and histamine[8]; it has antioxidant properties[9]; it inhibits the synthesis of prostaglandins and thromboxanes, reducing platelet and erythrocyte aggregation, as well as blood viscosity.[10,11] In animal models, calcium dobesilate reduces experimental lymphedema[12] and intralymphatic pressure,[13] increases lymphatic flow,[14] and decreases angiogenesis,[15] carboxymethyl-lysine-advanced glycation end product formation, and vascular endothelial cell growth factor overexpression, as well as albumin leakage.[16]

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The safety and efficacy of calcium dobesilate has been shown in several clinical trials. Double-blind, placebo-controlled trials have shown improvement in symptoms, such as pain, cramps, heavy legs, itching, and paraesthesia, as well as reduction in the leg volume.[17-19] The safety of calcium dobesilate was reviewed using international literature and postmarketing surveillance; the most frequent adverse events were fever, gastrointestinal disorders, and skin reactions.[20]

The aims of the present trial were to show the lymphagogue effect of calcium dobesilate, as well as to show the effect of calcium dobesilate in the lymphovenous edema.

Patients and Methods

It was a randomized, placebo-controlled, double-blind clinical trial. Patients, men and women, aged > 25 years with lymphovenous vascular edema (CVD) were included. The exclusion criteria were pregnancy, breast feeding, diabetes mellitus, neuropathy, oral or parenteral contraceptives, leg injuries, postphlebitic syndrome, current treatment with other antivaricose drug or diuretics or steroids, and patients to surgical correction or sclerotherapy of CVI. Patients with traumatic or degenerative arthritis were not included. Patients with secondary venous disease, such as obstruction or valvular failure, were excluded by duplex color scanning and venous plethysmography. The severity of the CVI was classified on the scale of Widmer[21] from grade I to V.

Patients were randomized after they had signed the written informed consent form. They had a lead in/wash out period without treatment for 7 days before the beginning of trial medication. Patients received 1 capsule of calcium dobesilate 500 mg Doxium 500 (OM PHARMA, Meyrin/Geneva, Switzerland) every 8 hours (1.5 g/day) or placebo by 49 days.

The medical history and the physical examination were carried out at the first visit. Patients also had safety laboratory tests (blood cytology, blood chemistry, and urinalysis), as well as venous plethysmogaphy, radioisotopic lymphography, dupplex test, and perimetry of leg, calf, and ankle in both lower limbs (second visit). After the first visit, the patients attended to clinical visit on days 7 (beginning of treatment, visit 2), 21, 35, 46, and 56 (end of the treatment, visit 5). Patients had an additional safety visit on day 63.

Dupplex test (Esaote Biomedica, model Bisound Genesis CFM 7,000 high resolution, Genova, Italy) was used to study the venous wall (classifying as normal or engrossed) and the valvular dysfunction (absent or present). It was performed on visits 2 and 5.

Venous plethysmography was used to (computerized, pneumatic plethymograph, Parks Electronics Systems model 008408, Aloha, Oregon) evaluate the venous output or outflow as normal (0-2 seconds) and abnormal (>2 seconds), and the recuperation time as normal (0-1 seconds), suspicious (1-3 seconds), abnormal (>4 seconds). It was performed on visits 2 and 5.

Radioisotopic lymphogammagraphy was carried out (visit 2 and 5) as follows. Two millicuries of rhenium sulfur with technetium 99 in a volume <0.55 mL were injected subcutaneously in the first interdigital space of the foot. Scintigraphic images were obtained using a gamma-camera (General Electric 400T, GE medical systems, Milwaukee, Wisconsin), multiplanar with SPECT (single photon emission tomography). This method assesses the capture of radioactive material and the speed of the lymphatic flow. The capture index was graded as normal (100%-85%), mild alteration (84%-75%), moderate alteration (74%-50%), severe alteration (49%-25%), and very severe alteration (<25%). The speed of lymphatic flow was regarded as normal (7 minutes), slow mild (8-10 minutes), slow moderate (11-12 minutes), slow severe (>13 minutes); accelerated mild (4-6 minutes), accelerated moderate (2-3 minutes), and accelerated severe (<2 minutes).

Perimetry of leg, calf, and ankle was realized on visits 2, 3, 4, and 5. Regarding symptoms, pain, was classified as absent, mild, moderate, and severe at the same times. The outcomes of the investigator's global evaluation were classified as improvement, without improvement (minimal changes), no changes, and worsening (visit 5).

The trial was conducted in the Vascular Institute of the Clinica de Diagnostico Medico (CEDIME) in Merida, Yucatan, Mexico. Local Ethics Committee approved protocol, case report form, and written informed consent. Statistical analyses comprise the calculation of frequencies, mean and standard deviation, and comparisons with χ^2 test, Student *t* test, Wilcoxon test, and analysis of variance for repeated measures.

Results

Forty-nine patients were included, with 25 being randomized to calcium dobesilate and 24 to placebo.

The characteristics of the patients are given in Table 1. The findings on the physical examination of lower limbs at the beginning of the study are

Table 1. Characteristics of the Patients

	Calcium Dobesilate	Placebo
Sex (male/female)	2/23	3/21
Age (y, mean ± SD)	53.6 ± 8.1	50.7 ± 8.7
Weight (kg, mean ± SD)	73.2 ± 14.4	70.0 ± 14.41
Height (m, mean ± SD)	1.58 ± 0.08	1.58 ± 0.09
Time of evolution (y, mean ± SD)	18.2 ± 15.6	15.0 ± 16.7
Widmer classification (n, %)		
IB (%)	3, 12	0, 0
IC (%)	3, 12	8, 33.3
II (%)	8, 32	8, 33.3
III (%)	5, 20	5, 20.8
IV (%)	6, 24	3, 12.5

NOTE: SD = standard deviation.

Table 2. Findings of Examination of the Lower Limbs of the Patients

Signs (n,%)	Calcium Dobesilate (%)	Placebo (%)
Telangectasias	5, 20	8, 33.3
Varices	16, 64	15, 62.5
Edema	19, 76	22, 91.7
Induration	8, 32	2, 8.3
Ulcer	8, 32	5, 20.8
Hyperpigmentation	12, 48	12, 50
Pain to touch	7, 28	5, 20.8
Lymphorhage	1, 4	1, 4.2
Skin atrophy	1, 4	0, 0

described in Table 2. At the end of the study, the perimeter of leg, calf, and ankle presented small but with significant changes in the calcium dobesilate group, which was not the case for the placebo group. For instance, in the left leg, the perimeter changed from 51.2 ± 6.1 cm to 50.3 ± 5.6 cm; left calf from 40.6 ± 4.6 cm to 39.0 ± 4.6 cm; left ankle from 36.2 ± 4.5 cm to 33.6 ± 3.8 cm in the calcium dobesilate group ($P < .05$ for each comparison pair), whereas the respective changes in the placebo group were from 48.4 ± 3.9 cm to 48.1 ± 3.9; from 39.7 ± 2.2 cm to 39.7 ± 2.4 cm; from 35.9 ± 3.7 to 35.6 ± 3.8 cm ($P > .05$ for each comparison pair).

Evolution of pain severity is presented in Figure 1. By the end of the trial, most of the patients on calcium dobesilate did not present any pain (68% vs 0% in the placebo group, $P < .001$ by χ^2). Figure 2 shows the capture index in the left lower limb lymphogammagraphy, and Figure 3 shows the speed of lymph flow in the left lower limb lymphogammagraphy, both at baseline and at the end of the trial; Figure 4 shows examples of lymphogammagraphy in patients with improvement in

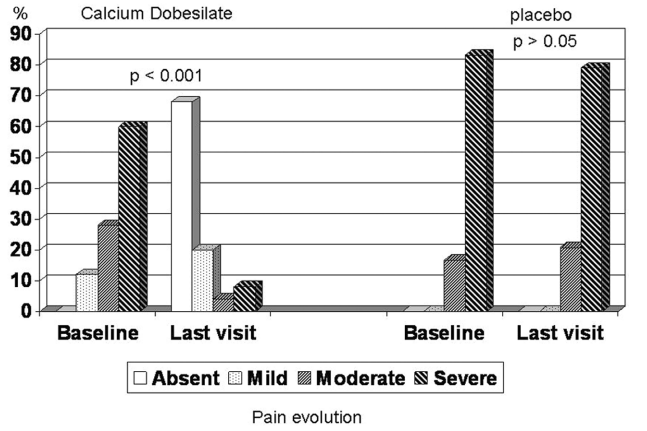

Figure 1. Pain evolution. The figure depicts the frequency of absent, mild, moderate, and severe pain at baseline and at the final visit in the calcium dobesilate and placebo groups.

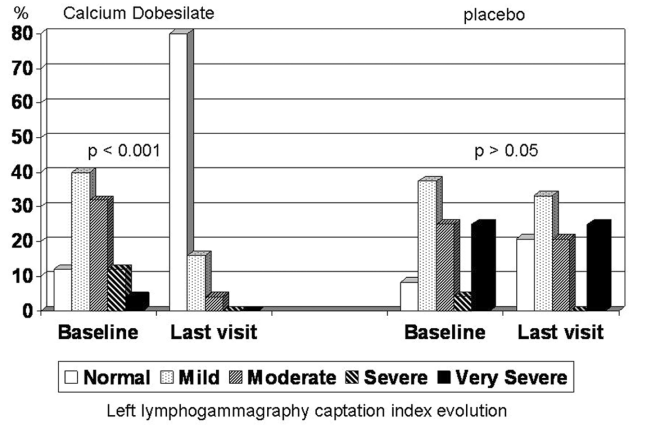

Figure 2. Capture index evolution in the left lymphogammagraphy. The figure depicts the frequency of absent, mild, moderate, and severe alteration of capture index at baseline and at the final visit in the calcium dobesilate and placebo groups.

lymph flow. In most of the cases, calcium dobesilate-treated patients had a normalization of capture index and speed of lymph flow (80% and 78%, respectively). In both investigations, only the calcium dobesilate group showed improvement ($P < .001$ by χ^2).

At the end of the study, baseline duplex test did not find significant alterations in valve function, blood flow, and thickness of the venous wall in both groups. Plethysmography did not show alterations in flow, as well as in recuperation time. These evaluations were not performed again.

According to the investigator, 22 out of 25 (88%) calcium dobesilate-treated patients presented clinical improvement, and only 5 out of 24 (20.8%) had such improvement in the placebo group.

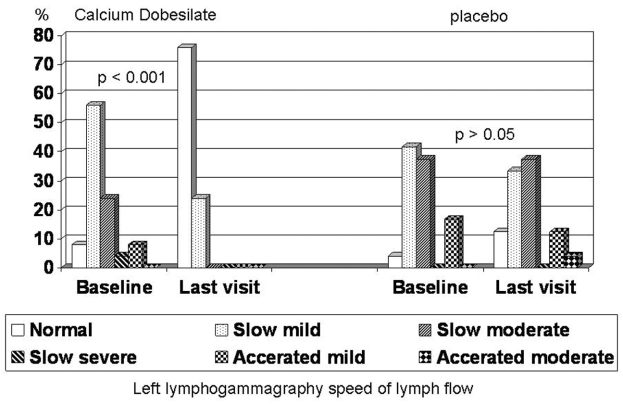

Figure 3. Speed of lymph flow in the left lymphogammagraphy. The figure depicts the frequency normal, slow mild, slow moderate, slow severe, mild accelerated, moderate accelerated flow at baseline and at the final visit in the calcium dobesilate and placebo groups.

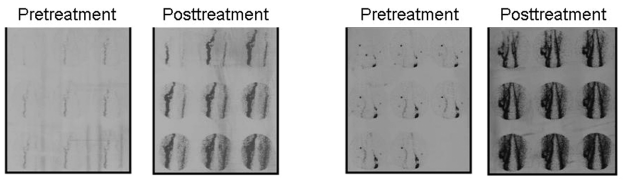

Figure 4. Examples of lymphogammagraphy in patients with improvement in lymph flow; pretreatment and posttreatment. The darker color corresponds to lymph.

There were only 2 adverse events related to the trial drugs; 1 patient on calcium dobesilate developed rash, and 1 patient on placebo complained of vomiting.

Discussion

The use of venotonic medications for the symptomatic treatment of CVI is controversial, for example, a Cochrane systematic review[6] points to some efficacy of phlebotonics on edema with uncertain clinical relevance. However, a consensus of an expert meeting held during a conference of the European Society for Clinical Hemorheology[5] concluded that venoactive drugs are effective and may be applied in mild to moderate CVD. A metaanalysis of clinical trials with calcium dobesilate found that it is significantly more effective than placebo to induce remission of symptoms in CVI, such as, lower limb pain, leg heaviness, cramps, and parasthesia.[22]

Safety of calcium dobesilate has also been studied in a review considering adverse events reports in clinical trials and postmarketing surveillance. The most frequent adverse events with calcium dobesilate were fever, gastrointestinal disorders, and skin reactions. Some cases of agranulocytosis were associated to the use of calcium dobesilate, but the estimated rate of prevalence of this disorder was 0.32 cases/million of treated patients, which is 10 times lower than the prevalence of agranulocytosis in the general population.[20]

In the present trial it was shown that patients suffering from CVD had alterations in the lymph flow and that calcium dobesilate has an important impact in the lymph physiology as it improved the capture of elements in the extracellular space and normalized the lymph flow.

Because of the limitations of current evidence, there is a need for further randomized, controlled clinical trials with greater attention paid to methodological quality.

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