Scientific Research Publishing

International Journal of Clinical Medicine, 2024, 15, 211-223
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Double-Blind, Parallel Group Study to Compare the Clinical Effectiveness of Calcium Dobesilate 500 mg BID vs. Calcium Dobesilate LP 1 g OD, in Patients with Chronic Venous Insufficiency of the Lower Limbs

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How to cite this paper: Téllez Méndez, R., González Yibirin, M. and Rincón Matute, D. (2024) Double-Blind, Parallel Group Study to Compare the Clinical Effectiveness of Calcium Dobesilate 500 mg BID vs. Calcium Dobesilate LP 1 g OD, in Patients with Chronic Venous Insufficiency of the Lower Limbs. *International Journal of Clinical Medicine*, **15**, 211-223.
https://doi.org/10.4236/ijcm.2024.155015

Received: April 9, 2024
Accepted: May 27, 2024
Published: May 30, 2024

Abstract

Background: Chronic venous insufficiency (CVI) describes a condition that affects the venous system of the lower extremities due to venous hypertension (VH. The prevalence is between 5% - 30%. CVI is associated with older age, smoking, lower extremity trauma, presence of an arteriovenous shunt, and elevated estrogen levels. All patients should be initially treated with conservative management. Venoactive drugs like calcium dobesilate are useful. **Objectives:** The primary objective compared the clinical improvement in patients with CVI, grades 0 - 3 of the CEAP classification of chronic venous disease, produced by two formulations of calcium dobesilate: calcium dobesilate LP 1 g OD vs calcium dobesilate 500 mg BID, immediate release. The secondary objective assessed the side effects of both formulations. **Method:** All patients took one tablet and one capsule at 7 am, and one capsule at 7 pm, for 8 weeks. One group received dobesilate 1 g OD and the other group received dobesilate 500 md BID. They were evaluated after 15, 30 and 60 days of treatment, using the symptom evaluation scale. **Results:** In both groups, there was a significant decrease in the symptom score after 15 days. Four patients in the Dobesilate OD group: had adverse effects, which did not require suspension of treatment. In the BID dobesilate group, there was one therapeutic failure, and one case of gastric discomfort. **Conclusions:** Prolonged-release Calcium dobesilate 1 g OD is as effective as calcium dobesilate 500 mg BID for the treatment of patients with chronic venous insufficiency.

Keywords

Chronic Venous Insufficiency (CVI), Calcium Dobesilate, CEAP Classification, Adverse Effects, Treatment Adherence

1. Introduction

The term chronic venous insufficiency (CVI) describes a condition that affects the venous system of the lower extremities due to venous hypertension (VH), which causes symptoms such as pain, inflammation, edema, skin changes and ulcerations. CVI, with its diverse clinical spectrum, is a relatively common medical problem often overlooked due to underestimation of the magnitude and impact of the problem, as well as incomplete recognition of the various presenting manifestations of primary and secondary venous disorders. [1]

Several prospective epidemiological studies have shown that CVI is progressive. In a study, 740 children between 10 and 12 years of age without any CVD were observed every five years for a total of 20 years, and were evaluated by clinical, Doppler ultrasound and recharge time of photoplethysmography for reflux. It was found that there was a gradual increase in the presence of reflux from 2.4% to 20.6%, accompanied by an increase in trunk varicose veins from 0% to 11%. The manifestation of a truncal varicose vein was preceded by reflux in the same vein, reflux that began predominantly in the saphenofemoral region and saphenopopliteal junctions; the onset of reflux was around puberty; and preclinical reflux represented a 30% risk of developing truncal varicose veins in four years. [2]

Varicose veins have an estimated prevalence between 5% and 30% in the adult population, with a female predominance of 3 to 1, although a recent study has determined a higher prevalence in men. [3] In the Edinburgh Study with 1566 subjects evaluated with duplex ultrasound, they found CVI in 9.4% of men and 6.6% of women, which after adjusting for age increased significantly in men (21.2% in men > 50 years of age, and 12.0% in women > 50 years of age). [4]

In the San Valentino Vascular Screening project, they found among the 30,000 subjects evaluated by clinic and duplex ultrasound, a prevalence of 7% for varicose veins and 0.86% for "symptomatic" CVI. [5] As in previous studies, CVI was more common with age, but there was no significant gender difference. The rate of development of varicose veins can be estimated from the Framingham Heart Study, where there is an annual incidence of 2.6% in women and 1.9% in men with risk factors. [6] The prevalence in the world is expected to increase, given the possible underdiagnoses of CVI, the increase in obesity and the aging of the population. [1]

As we can see, factors influencing the wide range of estimated prevalence include older age, smoking, lower extremity trauma, presence of an arteriovenous shunt, elevated estrogen levels [7], sex, family history of varicose veins, obesity,

pregnancy, phlebitis, and previous leg injuries. [8] [9] Standing and perhaps sitting may also be environmental or behavioral factors associated with CVI. [6] [7] [8] [9]

In CVI, venous valve reflux, obstruction of venous flow, or both cause VH. [10] These mechanisms produce VH, particularly from standing or walking. The venous pressure of the foot veins in the resting position without contraction of the skeletal muscle, reaches between 80 and 90 mmHg. In a subject with competent venous valves, this pressure decreases to less than 30 mmHg during ambulation. [11] However, in a patient with CVI, the decrease in venous pressure with leg movements is minor. If the valves of the perforating veins are incompetent, the VH generated in the deep veins by the contraction of the calf muscles can be transmitted to the superficial system and the microcirculation of the skin, contributing with these hemodynamic alterations to the alterations in the microcirculation. [12] [13] These changes can lead to dermal changes with hyperpigmentation, fibrosis of the subcutaneous tissue ("lipodermatosclerosis"), and eventual ulceration.

This pathology represents a spectrum of diseases ranging from simple telangiectasias or reticular veins to more advanced stages, such as skin fibrosis and venous ulcers. Post-thrombotic syndrome after deep vein thrombosis (DVT) also causes VH due to the remaining obstruction of venous outflow and valvular reflux due to valvular damage. [14]

All patients with signs and/or symptoms of CVI should be initially treated with conservative management. The use of compression stockings is the basis of conservative treatment. However, risk modification should also be encouraged in the patient, such as weight reduction in an obese patient, regular walking exercise, and smoking cessation, as conservative treatment. [10]

Venoactive drugs may be considered for the treatment of symptomatic varicose veins, ankle edema, and venous ulcers. The principle for using these venoactive drugs is to improve venous tone and capillary permeability. [15] Calcium dobesilate is a venoactive synthetic drug that acts at the level of the capillary walls, regularizing disturbed physiological functions such as increased permeability and decreased resistance. [16] [17] At the level of the vascular wall, it inhibits the vasoactive substances responsible for the contracture or shortening of endothelial cells: bradykinin, histamine and serotonin, normalizing capillary permeability. It inhibits the enzymes that degrade mucopolysaccharides, components of the basement membrane, normalizing capillary resistance. It facilitates the cross-linking of collagenoid substances of the basement membrane by covalent calcium dobesilate-collagen bonds, normalizing capillary resistance and, at the level of the hematological system, it prevents the destruction of platelet membranes and its thrombogenic effect. It has an erythrocyte anti-agglutinating effect, improving blood viscosity, increasing erythrocyte elasticity and deformability, allowing better tissue irrigation, reducing the level of high-density plasma proteins, and decreasing plasma viscosity. On lymphatic flow, it increases return lymphatic flow, thereby obtaining an anti-edematous effect.

A review conducted in 2004 by Ciapponi et al. found that there was no significant difference between patients receiving 1,500 mg/day of calcium dobesilate and those receiving 1,000 mg/day, demonstrating that the daily dose of 1,000 mg (1 g) per day is effective and safe for the treatment of CVI. [18] Several studies have evaluated the use of calcium dobesilate against placebo for periods of 7 to 9 weeks. [19] [20] [21]

A once-daily extended-release (LP) formulation of calcium dobesilate has been developed with the aim of improving compliance and therefore the effectiveness of the treatment. The pharmacokinetic study carried out demonstrated that Calcium Dobesilate LP at a daily dose of 1 g is absorbed at the same rate measured by Cmax and in an amount measured by AUC, similar to the dose of 500 mg, administered BID. [22]

2. Objectives

The primary objective of this study is to compare the clinical improvement in patients with CVI grades 0 - 3 of the CEAP classification (Clinical-Etiological-Anatomical-Pathophysiological) of chronic venous disease [23], produced by two formulations of calcium dobesilate: calcium dobesilate LP 1 g OD vs calcium dobesilate 500 mg BID, immediate release.

The secondary objective was to compare the appearance of adverse effects with the use of both treatment regimens and the possible effect of them on adherence to treatment.

3. Materials and Methods

3.1. Inclusion Criteria

Patients of both sexes, over 18 years of age, after having signed the informed consent approved by the Institutional Ethics Committee with a diagnosis of chronic venous insufficiency, classified between CEAP functional classes **C0** and **C3** (Table 1).

3.2. Exclusion Criteria

Previous diagnosis of superficial or deep vein thrombosis; secondary venous insufficiency including history of deep vein thrombosis; previous diagnosis of primary venous reflux of deep veins; history of venous extraction or phlebectomy, any sclerosing injection within 6 months prior to inclusion.

Edema of any non-venous etiology, including chronic heart failure, liver disease, kidney disease, lymphatic pathology, iatrogenic (calcium blockers), and hypersensitivity.

Allergy or intolerance to calcium dobesilate, or any component of the formulation.

Intake of venotonic treatments, triptans, diuretics, calcium antagonists, beta-blockers, ACE inhibitors and/or vasodilators and/or vasoconstrictors, in the month before the inclusion visit, NSAIDs, corticosteroids, ergotamine, dihydroergotamine

Table 1. Clinical classification (C) according to CEAP.

Class	Clinical Signs
C_0	No visible or palpable signs of venous incompetence
C_1	Spider veins and/or reticular varices
C_2	Varicose veins
C_3	Oedema
C_{4a}	Pigmentation, eczema
C_{4b}	Atrophie blanche, dermatoliposclerosis
C_5	Cured venous leg ulcer
C_6	Active venous leg ulcer

or any ergot alkaloid, vitamin C, nutraceutical products or phytotherapy with potential venotonic effect, or use of compression bandages within 2 weeks before the inclusion visit.

BMI greater than or equal to 30, underlying arterial disease, history of pulmonary embolism, pregnant or breastfeeding women.

4. Methods

It was a phase III study: randomized, double-blind, double-false, parallel-group. At the beginning, a medical history, complete physical examination and laboratory tests were performed; if the volunteers met the inclusion and not the exclusion criteria, and had signed the informed subject consent, they began treatment. All patients took one tablet and one capsule at 7 am and one capsule at 7 pm, for 8 weeks. One group received a 1 g Calcium Dobesilate LP active tablet and Calcium Dobesilate placebo, 500 mg capsules. The other group received a placebo Calcium Dobesilate LP 1 g tablet and Calcium Dobesilate active, 500 mg capsules. Controls were carried out after 15, 30 and 60 days of treatment, using the symptom evaluation scale (**Table 2**). Symptoms traditionally ascribed to chronic venous disease include aching, heaviness, a feeling of swelling, cramps, itching, tingling, and restless legs. [11] The clinical study by Arceo et al (2002) evaluated pain, paresthesia, edema, cramps, and heaviness to evaluate the efficacy of calcium dobesilate, the same clinical parameters we used. [21] The scale used in our study only included the parameters that could be present in patients classified between CEAP functional classes C0 and C3.

All patients who took the medication dose and had at least one post-treatment evaluation were included in the efficacy evaluation (intention-to-treat principle). The investigators applied the statistical method of descriptive analysis of the data; the normally distributed variables were compared using paired Student's t (within groups) and unpaired (between groups). Non-parametric variables were analyzed using Wilcoxon signed rank test (within group) and Mann Whitney U test between groups. An α error of 0.05 gave the study a power of 80% to detect a difference between the groups, for which, according to the calculation, 60 pa-

tients per group were required.

5. Results

In the anthropometric variables, personal and family history, there was an increase in weight at the end of the study of the patients in the BID dobesilate group.

The high blood pressure was the most notable antecedent (Table 3). Changes in systolic blood pressure had no clinical significance (Table 4). There was a significant decrease in the scores of all the symptoms evaluated, similar in both groups (Table 5; Figure 1). There were four patients with adverse effects in the Dobesilate OD group: headache, arthritis, hemorrhoids and skin rash; the adverse effects were mild and did not require suspension of treatment. In the BID dobesilate group, there was one therapeutic failure, two cases of Malaise and one case of gastric discomfort and the patients spontaneously discontinued treatment (Table 6).

Table 2. Symptom evaluation table in the evaluations of patients with CVI (Absent = 0, Mild = 1 Moderate = 2 Severe = 3).

Symptom	Absent	Mild	Moderate	Severe
Pain	Absent	Does not restrict activity or require treatment	Occasional activity limitation or pain	Severe activity limitation or pain
Paresthesia	Absent	At night	During the afternoon	During the morning
Edema	Absent	At night	During the afternoon	During the morning
Cramps	Absent	At night	During the afternoon	During the morning
Heaviness	Absent	At night	During the afternoon	During the morning

Table 3. Description of the evaluated population. Anthropomorphic variables and background.

Variable	Dobesilato OD	p intra groups	Dobesilato BID	p intra groups	P between groups
Age (years)	37.5 ± 7.6		38.2 ± 9.5		0.70**
Sex	58/6		65/5		0.89**
Initial weight (kg)	66.5 ± 11.0		68.8 ± 12.0		0.37**
Final Weight (kg)	65.6 ± 10.2	0.38*	71.8 ± 10.6	0.56*	0.01**
Height (m)	1.6 ± 0.1		1.6 ± 0.1		0.7**
Personal and family history					
Cesarean sections	48.4%		40.0%		
Arterial hypertension	57.8%		64.3%		

Continued

Diabetes	23.4%	25.7%
Cancer	18.8%	8.6%
Cardiovascular disease	20.3%	8.6%

*Wilcoxon signed-rank test; **Mann-Whitney U test.

Table 4. Hemodynamic variables.

Variable	Dobesilato OD	p intra groups	Dobesilato BID	p intra groups	P between groups
SAP mmHg					
Day 0	111.9 ± 11.5		112.6 ± 12.2		0.66**
2 weeks	112.1 ± 9.3	0.68*	113.5 ± 11.2	0.89*	0.72**
4 weeks	111.0 15.8	0.46*	114.2 ± 10.4	0.56*	0.16**
8 weeks	113.8 ± 7.3	0.14*	112.1 ± 9.7	0.20*	0.57**
DAP mmHg					
Day 0	71.2 ± 9.3		75.4 ± 9.6		0.03**
2 weeks	70.0 ± 8.2	0.27*	72.7 ± 7.4	0.15*	0.03**
4 weeks	71.4 ± 7.5	0.30*	74.3 ± 9.1	0.26*	0.07**
8 weeks	71.2 ± 6.6	0.99*	73.7 ± 9.1	0.47*	0.26**
Pulse bpm					
Day 0	67.0 ± 7.3		68.0 ± 6.0		0.35**
2 weeks	65.5 ± 5.3	0.12*	67.3 ± 6.0	0.38*	0.14**
4 weeks	66.4 ± 6.8	0.54*	67.6 ± 6.5	0.63*	0.36**
8 weeks	66.6 ± 8.2	0.44*	66.9 ± 7.3	0.80*	0.65**

SAP: Systolic Arterial Pressure. DAP: Diastolic Arterial Pressure. bpm: beats per minute. *Wilcoxon signed-rank test; **Mann-Whitney U test.

Table 5. Evolution of the evaluation variables.

	Dobesilato OD				Dobesilato BID			
	Day 0	**2 weeks**	**4 weeks**	**8 weeks**	**Day 0**	**2 weeks**	**4 weeks**	**8 weeks**
Pain	5.4 ± 2.7	3.2 ± 2.0	2.1 ± 1.6	1.3 ± 1.8	5.5 ± 2.3	3.5 ± 2.0	2.8 ± 1.8	2.0 ± 1.6
p intra groups		0.00	0.00	0.00		0.00	0.00	0.00
p between groups	0.99	0.40	0.04	0.02				
Paresthesia	5.0 ± 2.8	2.9 ± 2.1	1.8 ± 1.6	1.1 ± 1.3	5.0 ± 2.5	3.0 ± 2.1	2.2 ± 1.9	1.3 ± 1.5
p intra groups*		0.00	0.00	0.00		0.00	0.00	0.00
p between groups**	0.92	0.95	0.22	0.33				

Continued

Edema	4.6 ± 3.2	2.8 ± 2.6	2.0 ± 2.2	1.4 ± 1.8	4.3 ± 2.9	2.6 ± 2.3	1.9 ± 1.9	1.2 ± 1.6
p intra groups*		0.00	0.00	0.02		0.00	0.00	0.00
p between groups**	0.54	0.84	0.75	0.94				
Cramps	5.4 ± 3.1	2.8 ± 2.4	1.9 ± 1.8	1.2 ± 1.6	5.7 ± 3.0	3.3 ± 2.4	2.6 ± 2.2	1.6 ± 1.9
p intra groups*		0.00	0.00	0.00		0.00	0.00	0.00
p between groups**	0.69	0.16	0.13	0.46				
Heaviness	6.2 ± 2.7	4.2 ± 2.2	2.6 ± 2.0	1.7 ± 2.0	6.1 ± 2.7	3.9 ± 2.4	3.0 ± 2.2	2.2 ± 2.1
p intra groups*		0.00	0.00	0.00		0.00	0.00	0.00
p between groups**	0.83	0.79	0.23	0.10				
Total	26.4 ± 10.5	15.8 ± 7.8	10.2 ± 6.4	5.0 ± 6.3	26.5 ± 9.2	15.8 ± 8.8	11.5 ± 8.2	7.1 ± 7.4
p intra groups*		0.00	0.00	0.00		0.00	0.00	0.00
p between groups**	0.80	0.77	0.38	0.05				

*Wilcoxon signed-rank test; **Mann-Whitney U test.

Table 6. Adverse effects.

Dobesilate OD group	Graduation	Consequence on treatment	Dobesilate BID group	Graduation	Consequence on treatment
Headache	Moderate	Not suspended	Therapeutic failure	Moderate	Suspended
Arthritis	Mild	Not suspended	Malaise	Moderate	Suspended
Hemorrhoids	Mild	Not suspended	Malaise	Moderate	Suspended
Skin rash	Mild	Not suspended	Gastric discomfort	Moderate	Suspended

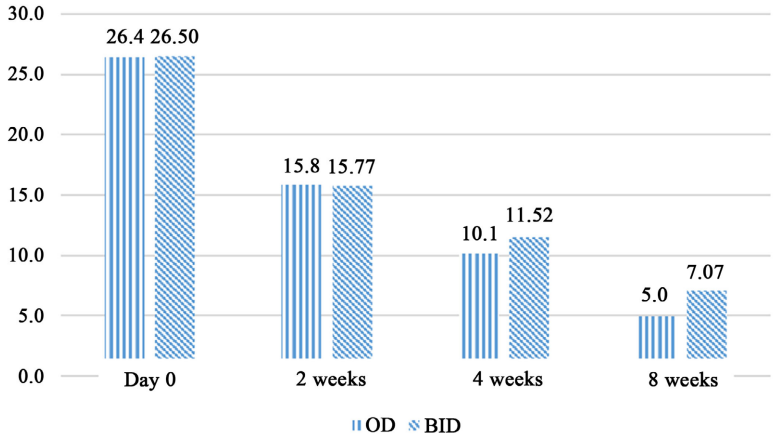

Figure 1. Evolution of symptoms, totals by group.

6. Discussion

Varicose veins are a common manifestation of CVI and are believed to result from remodeling of the venous wall. The veins of patients with varicose veins have different elastic properties than those of people without varicose veins. [24] [25] They are associated with hypertrophy of the venous wall, with greater collagen content, fragmentation of elastin fibers, and degradation and accumulation of extracellular matrix in the vein. [26] [27] [28] [29]

Several studies have shown that calcium dobesilate reduces the symptoms of venous insufficiency by reducing pain, edema and heaviness, with very good tolerance. [30]-[35]

The rationale for this study was to demonstrate that a 1g modified release formulation of Calcium Dobesilate (DoxiumBI®), administered once daily, would be equally effective as traditional doses of 500 mg twice daily in improving symptoms of peripheral venous insufficiency of the lower limbs. Studies have shown that reducing the number of daily intakes of a medication improves compliance and therefore its effectiveness, especially in long-term therapies. Among the causes of lack of adherence to treatment derived from the drug are cultural issues, chronic processes, polypharmacy, complicated dosing schedules, administration route that requires trained personnel or medication that exhibits significant adverse events. [36] [37] [38] [39] [40] Reducing the number of daily doses, we make the scheme simpler and easier to comply.

Our results showed no statistical differences in the evolution of the clinical parameters evaluated, except with pain, where there was a significant statistical difference at 4 and 8 weeks evaluations, in favor of the 1 g OD formulation. There was also a statistical difference in the total score evaluation at 8 weeks, in favor of the 1 g OD formulation.

Although the number of adverse effects was small, four reported in each group, the four patients who presented adverse events in the 500 mg, twice-daily group suspended the treatment due to them. The patients who received 1 g once daily did not suspend the treatment due to the adverse effects.

Lack of adherence to pharmacological treatment or therapeutic non-compliance is a prevalent and relevant problem in clinical practice. It is recommended to take into account the desire of patients to minimize the amount of medication they take, ask patients their concerns about the medication (adverse effects or risk of dependence), and discuss with the patient about how to incorporate taking medication into their daily routine or about possible non-pharmacological alternatives, among other factors. A formulation that is administered only once a day and that guarantees the same effectiveness will improve compliance with therapy.

7. Conclusions

This study showed that, in both groups, there was improvement in all symptoms: pain, paresthesia, cramp, edema and heaviness from the first 15 days of

treatment, and this improvement continued in the 30- and 60-day evaluations, increasing in each evaluation period, showing that both dosage forms have similar effectiveness and tolerability.

The incidence of adverse events was similar in both groups, but these events obliged the patients to suspend the treatment in the 500 mg, twice-daily group and not in the 1 g OD group.

The results of our study let us conclude that the use of a 1 g modified release formulation of Calcium Dobesilate (DoxiumBI®), administered once daily represents an advantage in the treatment of CVI since we obtained similar improvements when compared to a 500 mg, twice daily formulation. The incidence of adverse events with the 1g modified release formulation of Calcium Dobesilate, once daily was similar, but didn't require suspension of the treatment, as happened with the 500mg formulation. In brief, these results show that the use of a 1 g modified release formulation of Calcium Dobesilate, administered once daily, can improve the adherence to treatment of patients with CVI, just having to take one dose daily, with similar results and security.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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