Original article

Calcium dobesilate in patients suffering from chronic venous insufficiency: a double-blind, placebo-controlled, clinical trial

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Abstract

***Objective*:** To test the efficacy of calcium dobesilate (CaD) in chronic venous insufficiency (CVI).

***Method*:** Double-blind, parallel groups, placebo-controlled, multicentre trial in adult patients with symptomatic CVI and pitting oedema. Wearing of compression stockings Class II was admitted. During treatment period of eight weeks, the patients received CaD 3×500 mg/day or placebo. The leg volume calculation was based on a truncated cone model.

***Results*:** A total of 256 patients was randomized to treatment (dobesilate: $n = 132$, placebo: $n = 124$); the demographic and anamnestic data at admission were comparable in the two therapeutic groups. The volume of the lower calf diminished in the dobesilate group at the end of the active treatment period by $-64.72 \pm 111.93\ cm^3$ (mean $\pm$ SD), independent of the concomitant usage of compression stockings versus placebo $+0.8 \pm 152.98\ cm^3$ ($P = 0.0002$). The symptoms of pain, discomfort, heavy legs, tired legs, tingling, itching and cramps, as well as the global assessments by investigators and patients, also improved significantly ($P < 0.05$) better in the dobesilate group at the end of the treatment. The observed adverse events correspond to the known profile.

***Conclusion*:** Dobesilate reduces leg oedema and improves the symptoms of objectively diagnosed CVI, independent of the concomitant usage of compression stockings.

Keywords: randomized controlled trial; chronic venous insufficiency; drug treatment; calcium dobesilate

Introduction

Chronic venous insufficiency (CVI) is an underestimated public health problem affecting all industrialized countries; estimates of the prevalence of varicose veins vary widely reflecting differences in study populations including age, race, risk factors and gender, methods of measurement and disease definition.[1] The signs and symptoms range from mild leg heaviness or aching, dilated or unsightly veins, or troublesome oedema, to fibrosing subcutaneous panniculitis associated with recurrent cellulitis and chronic ulceration. These more severe manifestations are associated with repeated hospitalizations, high health-care costs and disability. CVI is a chronic disease which develops secondarily to haemodynamic abnormalities in the venous circulation. It is defined as clinical stages C3–C6 in the clinical, aetiological, anatomical and

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pathological elements (CEAP) classification.[2] Recent reports of prevalence of CVI vary from 4.5% to 13.6% for venous oedema (C3) and from 3.6% to 8.6% for skin changes including venous ulcers (C4–C6).[3] Prevalence estimates for varicose veins are between 21.8% and 29.4%.[3] Established risk factors include older age, female gender, pregnancy, family history of venous disease, obesity and occupations associated with orthostasis.[3] In an American study,[4] venous disease increased with age and was more common in Caucasians. Spider veins, varicose veins, superficial functional disease and superficial thrombotic events were more common in women than men, but trophic changes and deep functional disease were less common in women. It has been shown[5,6] that the presence of reflux correlates positively with increasing CVI grade of visible disease and that the presence of symptoms – particularly oedema – correlates almost always positively with both worsening of visible findings and of haemodynamic changes in both genders. In CVI, the venous hypertension and stasis leads to reflux to the capillaries resulting in ultrastructural changes capable of producing capillary hyperpermeability, which is responsible for transcapillary escape of fluid and tissue compression. In severe chronic venous incompetence there is not only microangiopathy of the blood capillaries, but also the superficial lymphatic skin capillaries at the medial ankle region are damaged. The network is interrupted by obliterations or may even be completely destroyed. Oedema formation results from increased permeability of blood capillaries and deficient lymphatic drainage of interstitial fluid.[7]

The criteria for conducting clinical trials in CVI have been defined by phlebological societies,[8] and thus represent a widespread consensus in Europe. Calcium dobesilate (calcium dihydroxy-2,5-benzenesulfonate – CaD) is a synthetic compound, which is known to be effective in microcirculatory disorders, by reducing the permeability of the capillary wall, inhibiting platelet aggregation and thrombus formation, lowering blood hyperviscosity and increasing red cell flexibility.[9] Several recent clinical trials[10–12] have dealt with dobesilate as a treatment for the relief of symptoms associated with chronic venous disease. However, they were not fully compliant with the above-mentioned criteria and they differ in their patient's selection, methodologies and outcomes studied. The study presented herein was set up according to currently accepted diagnostic and therapeutic criteria, in order to supersede the limitations of earlier studies.

Methods

Study protocol and participants

Outpatients of both sexes, aged 20–70 years, with pitting oedema due to CVI (C3–C5 according to the CEAP classification) and at least one of the symptoms such as discomfort and pain were recruited in 14 centres in Switzerland and Germany. The CVI diagnosis had to be confirmed by clinical examination and duplex sonography. Patients were investigated in the upright position in a standardized way for obstruction and/or reflux in the superficial and deep-venous system. Reflux was defined as retrograde flow >0.5 second. The main exclusion criteria were diseases that imitate the symptomatology of CVI, cardiac insufficiency, ulceration of the lower leg, diabetes mellitus, hypertension, lymphoedema, sclerotherapy during the last six months, lipoedema, obesity (BMI $>30\,kg/m^2$), diseases of the gastrointestinal tract, female patients who were pregnant, lactating or of childbearing potential and not protected from pregnancy by a sufficiently reliable method, malignant diseases. Wearing of compressive stockings Class II on a regular basis for the last three months was allowed, but should not be changed during the trial. Diuretics, venotropic medication, antiphlogistic drugs, corticosteroids, regular intake of analgetics and competing systemic/local drug treatments were not allowed during the study.

Study design, randomization and masking

The study was a randomized, double-blind, parallel group trial, including a two-week screening period, an eight-week treatment phase and a two-week follow-up phase without treatment. Patients were randomized to receive $3 \times 500\,mg$/day of CaD (Doxium®, OM PHARMA, Geneva, Switzerland) or matching placebo. Randomization with blocks of four was used. The randomization list was produced by an independent person. The study medication was packed in identical boxes marked with a randomization number; each newly randomized patient was given the medication with the lowest randomization number available. Compliance was checked by means of drug accountability (pill count). The study was performed in accordance with the latest revision of the Declaration of Helsinki, local law and good clinical practice. The study protocol was reviewed by the ethics committee of all centres and a written informed consent was available from all patients. The study progress was monitored by a clinical research organization.

Outcome measures

The primary efficacy endpoint was the relative leg volume change after eight weeks treatment compared with baseline in the most pathological leg assessed by a volumetric measurement with a calibrated tape and calculated by assimilating the lower leg volume to a truncated cone.[13] This calculation is based on the measurement of the circumferences of the ankle and the calf of the most pathological leg with a calibrated spring-metered tape. Recently, this kind of measurement was compared with optoelectronic volumetry.[14] Although there was a constant difference between the two methods (yielded larger apparent circumferences with the optoelectronic volumetry), the results were comparable with the two methods. These measurements were performed by the same investigator (in each centre) and at the same time of day between 15:00 and 19:00, for each patient starting at baseline V2 and at the following visits V3, V4 and V5. The time of the measurement had to be recorded. Patients had to remain seated for 10 minutes before the measurements were made. The measurements had to be carried out in standing position, however, immediately after standing up. Secondary endpoints included the change of leg perimeters, the evaluation of the patient's subjective symptomatology (pain, discomfort, feeling of tired or heavy legs, tingling, itching and cramps) on a five-point categorical scale, and the assessment of the overall efficacy by the patient and investigator. For data reduction a symptom score was calculated as the unweighted sum of the single symptom items. Furthermore, pain and discomfort was assessed by means of 100 mm Visual Analogue Scales (VAS) and the quality of life was assessed using the chronic lower limb venous insufficiency (CIVIQ) score.[15,16]

Safety variables

Adverse events (AEs) were recorded at each visit, and haematology and clinical chemistry variables were assayed during the study.

Statistics and data analysis

The working hypothesis for this trial was that active treatment would be superior to placebo and that CaD would induce an average reduction of the leg volume. Assuming an effect size of -3.8% for CaD and -2.5% for placebo with a SD of 3.0%, a minimum of 85 patients were required to prove superiority with an α-error of 5% and a power of 80%. The analysis was based on the intention-to-treat (ITT) principle. According to the protocol, changes in the leg volume were tested by an analysis-of-variance factors 'study drug', 'centre' and the 'centre × treatment interaction'. Furthermore, the treatment differences were estimated by means of mean differences and corresponding 95% confidence intervals. Moreover, descriptive statistical methods were used for the analysis of secondary efficacy and safety variables.

Results

Flow of participants through study

A total of 304 patients were screened and 256 were randomized. The ITT population comprised all randomized patients with 132 in the CaD and 124 in the placebo group. The treatment groups were relatively well balanced with regard to background characteristics (Table 1). During the trial, 32 patients (CaD: $n = 23$) withdrew prematurely for the following reasons (numbers in parentheses refer to placebo patients, multiple citations possible): AEs 16 (3), inclusion/exclusion criteria violated 22 (6), withdrawal of consent 7 (3), lost to follow-up 0 (1), unsatisfactory efficacy 1 (0), other reasons 1 (0).

Table 1 Demographic data and baseline characteristics

	Calcium dobesilate ($n = 132$)	Placebo ($n = 124$)
Age (years) Mean (SD)	53.20 (11.52)	53.52 (12.14)
Height (cm) Mean (SD)	168.86 (7.82)	168.36 (7.17)
Weight (kg) Mean (SD)	73.80 (12.66)	72.55 (10.40)
BP systolic (mmHg) Mean (SD)	126.33 (15.01)	127.05 (16.35)
BP diastolic (mmHg) Mean (SD)	78.20 (9.54)	77.88 (9.24)
Sex (m/f) (%)	15.9/84.1	13.7/86.3
Compressive stockings (%)	28.0	25.8
Venous insufficiency operation (%)	51.5	53.2
Sclerotherapy (%)	32.6	41.9
CEAP class (%)		
3	53.8	59.7
4	41.7	37.1
5	4.5	3.2
Extent of standing position at work (%)		
<33	41.7	34.7
33–66	40.2	43.5
>66	18.2	21.8
Oedema due to acute inflammation can be excluded (%)	98.5	99.2

SD, standard deviation; CEAP, clinical, aetiological, anatomical and pathological elements

Compliance

The mean (+SD) global compliance over the treatment period was similar in both groups at visits three and four: CaD 93.1% (14.09%) and 94.4% (18.05%) versus placebo 97.0% (9.55%) and 95.9% (15.08%), respectively.

Outcome measures

The relative change of the leg volume after eight weeks of treatment from baseline was a reduction by 2.04 ± 3.4 % on average in the CaD treatment group compared with an increase of about 0.1 ± 4.8% in the placebo group. This treatment difference was statistically significant in favour of the active treatment (Table 2, Figure 1). The absolute leg volume changes were statistically different between CaD and placebo, too (Table 2). The results for the ankle and calf perimeters from which the leg volumes were derived are given in Table 3. There were no significant differences between the treatment groups regarding the changes from baseline to the end of treatment regarding the CIVIQ score (Table 3). On average, the pain at the most pathological leg assessed by VAS was reduced after eight weeks of treatment compared with baseline in both groups. However, the mean reduction in the CaD (10.2 mm, SD = 26.26 mm) group was significantly more pronounced than in the placebo group (0.92 mm, SD = 22.96 mm; $P = 0.0071$). A similar result was found for the discomfort at the most pathological leg assessed by VAS (CaD: 19.1 mm reduction, SD = 25.42 mm versus placebo: 10.2 mm, SD = 25.87 mm). The global assessment of efficacy by investigators and patients at the end of treatment showed significant differences between the two treatment groups in favour of the CaD treatment (Table 4).

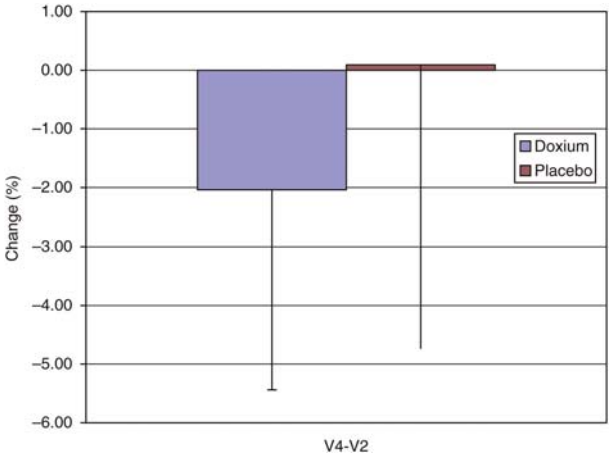

Figure 1 Relative leg volume change after eight weeks of treatment

Table 2 Leg volume change from baseline (V2) to the end of treatment (V4)

		Calcium dobesilate	Placebo
Relative leg volume change (%)			
N		120*	119*
Mean		−2.04	+0.09
SD		3.40	4.82
Mean treatment effect (%)		−2.13	
95% confidence interval		−3.20; −1.07	
		$P = 0.0001$	
Absolute leg volume change (cm^3)			
N		120*	119*
Mean		−64.72	+0.76
SD		111.93	152.98
Mean treatment effect (%)		−65.48	
95% confidence interval		−99.62; −31.34	
		$P = 0.0002$	
Relative leg volume change (%)			
Compressive stockings			
	Yes		
	N	35	30
	Mean	−2.59	+2.33
	SD	3.99	5.25
	No		
	N	85	88
	Mean	−1.82	−0.66
	SD	3.12	4.48

*Only patients with data on both visits are considered
SD, standard deviation

Safety

There were 80 and 38 predominantly mild–moderate AEs reported in 48 and 24 patients from the CaD and the placebo groups, respectively. The most frequent disorders were, by System Organ Class, 'gastrointestinal' (CaD 19.0% versus placebo 8.1%), followed by 'general' (11.4% versus 1.6%), and by 'skin and subcutaneous tissue' (3.8% versus 7.3%). When only the events possibly, probably or certainly related to the study drugs were considered, the counts were much lower (33 versus 10 AEs). The most common related AEs were gastrointestinal disorders (18 versus 4). There were six serious adverse events (SAEs) in four patients (5 versus 1) due to hospitalizations. A possible causal relationship was documented in two patients of the CaD

Table 3 Secondary efficacy variables

	Calcium dobesilate			Placebo		
	V2	V4	V5	V2	V4	V5
Volume (cm^3)						
n	132	120	109	124	119	115
Mean	3088.36	3039.08	3049.88	3061.98	3073.38	3022.33
SD	518.53	517.96	517.88	514.16	527.01	485.90
Calf: Max. circumference (cm)						
N	132	120	109	124	119	115
Mean	39.13	38.80	38.88	38.88	38.91	38.64
SD	3.54	3.54	3.49	3.24	3.42	3.17
Ankle: Min. circumference (cm)						
N	132	120	109	124	119	115
Mean	24.22	24.05	24.09	24.22	24.32	24.07
SD	2.14	2.13	2.13	2.38	2.26	2.18
Symptom score						
N	132	120	108	124	119	115
Mean	21.36	14.83	15.19	21.02	21.14	20.83
SD	11.32	11.97	12.49	9.56	11.11	11.91
Life questionnaire (CIVIC) score						
N	121	112	100	116	108	104
Mean	45.40	40.63	41.18	44.37	40.67	39.21
SD	15.15	16.33	17.67	13.60	13.14	12.84

Max. = maximum; Min. = minimum; CIVIQ, chronic lower limb venous insufficiency; SD = standard deviation

group (abdominal pain and gastroenteritis associated with arrhythmia and increased transaminases). There were no changes of clinical concern in vital signs and haematological and biochemical variables in both treatment groups. At visits three, four and five the tolerability was assessed globally by the investigators and patients as 'very good' or 'good' in most cases with no relevant differences between the treatments.

Discussion

Pondering on the existing evidence, a European consensus group concluded that 'veno-active drugs are effective and may be applied in case of symptomatic chronic venous disease; in some cases they may replace compression and/or complement its effects'.[17] However, an analysis of the Cochrane group concluded that 'there is not enough evidence to globally support the efficacy of phlebotonics for chronic venous insufficiency and that there is a need for further randomised, controlled clinical trials with greater attention paid to methodological quality'.[18] The study presented herein was conducted according to the currently accepted standards and confirms the efficacy of dobesilate in the management of symptomatic CVI.

Table 4 Global assessment of efficacy by investigators and patients at the end of treatment (visit 4)

	Investigators		Patients	
	Calcium dobesilate ($n = 123$)	Placebo ($n = 120$)	Calcium dobesilate ($n = 123$)	Placebo ($n = 120$)
Missing	2.4%	0.8%	2.4%	0.8%
Worsening	8.1%	13.3%	5.7%	14.9%
No change	40.7%	49.2%	36.6%	44.2%
Improvement	48.8%	36.7%	55.3%	40.0%
P	$P = 0.0125$		$P = 0.0045$	

The main variable studied in this trial was the reduction of the volume of the lower calf (ankle-calf) which was comparable at baseline between the study treatments. At the end of the active treatment the volume had been reduced with the active medication, while it rested almost unchanged in the placebo population. The placebo values fluctuated somewhat inconsistently. There were more patients lost in the dobesilate group but, assuming no change in the volume of the lower calf, the difference between treatments still is highly significant. Not included in this value is the volume of the foot, which approximately represents an additional 860 ± 150 mL.[19] There are three criteria which permit to conclude that this volume reduction is of clinical relevance:

(1) The volume reduction is calculated based on the total lower leg volume of approximately 3000 mL. Venous oedema, however, is located in the subcutaneous tissue which represents approximately 20% of the total leg volume or

600 mL.[20] Total volume reduction of 65 mL represents volume reduction in the subcutaneous layer of 10.8%. Taking into account that only one-third of the subcutis may be oedema, real oedema reduction reaches as much as 32.5%. This is a rough approximation as the results depend also on the thickness of the subcutaneous tissue and the extent of oedema formation;

(2) There is a reasonable degree of correlation between the reduction of the volume of the lower calf and the improvement of most symptoms rated;

(3) The reduction of the volume of the lower calf appears to be of the same order of magnitude as described for compression stockings Class I. Among patients in stage I (according to Widmer) where there was a mean reduction in lower calf volume of 35.3–38.1 mL after wearing support stockings or compression stockings Class I. Compression Class II stockings obtained a mean reduction in lower calf volume of 70.1 mL. In the group of patients in Widmer stage II the corresponding mean values were 34.6–54.4 mL and 66.0 mL, respectively. Interesting to note that, if all parameters were taken into account, the majority of patients would have chosen to use compression Class I products.[21]

In the current study there were two subpopulations already defined at randomization: the smaller group of patients with compression Class II stockings and the larger group of patients without. In both sub-populations the lower calf volume was reduced by dobesilate (Table 2). This finding is interesting because the patients with compression stockings continued to use them during the trial. The quality of life was only mildly impaired by the CVI in the population studied. Therefore, it is not surprising that only the pain subscore and the physical subscore showed a significant benefit of the dobesilate treatment. In the first two weeks of active medication there was an increased incidence of mainly gastrointestinal AEs with dobesilate, causing withdrawal of some patients. These AEs are known from the literature and the prescribing information.

Conclusion

The treatment with dobesilate during eight weeks of patients with symptomatic CVI, CEAP Class III, IV or V, and pitting oedema, was significantly more effective than placebo in reducing the oedema and the symptoms of venous disease. The efficacy of dobesilate was also confirmed in the subpopulation wearing compression stockings.

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