Original Article

COMPARATIVE STUDY OF CALCIUM DOBESILATE VERSUS PLACEBO IN CHRONIC VENOUS INSUFFICIENCY

Dr. Gaurav Nirwal [1], Dr. Abhishek Gaur [2], Dr. Diksha Agarawal [3*], Dr. Mukesh Saini [4], Dr. Bhupender [5]

[1]Department of General Surgery, Assistant Professor, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.
[2]Department of General Surgery, Associate Professor, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.
[3]Department of General Surgery, 3rd year PG resident, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.
[4]Department of General Surgery, Assistant Professor, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.
[5]Department of General Surgery, Assistant Professor, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.

Corresponding Author: Dr. Diksha Agarawal, [3]Department of General Surgery, 3rd year PG resident, Muzaffarnagar Medical College, Uttar Pradesh, India 251203.
EMAIL ID: agrawaldiksha712@gmail.com

DOI: 10.47750/pnr.2022.13.S09.1120

Abstract

Introduction: Chronic venous insufficiency (CVI) is the inability of veins to transport blood unidirectionally to the heart with flow consistent with tissue drainage, thermoregulatory and hemodynamic reserve needs, regardless of venous location or activity. Many randomized clinical trials (RCTs) have shown beneficial effects of calcium dobesilate.

Aims and Objective: Objective of the study was to compare the efficacy and effectiveness of calcium dobesilate versus placebo for chronic venous insufficiency.

Material and Methods: This present study was carried out in the Department of Surgery, Muzaffarnagar Medical College, Muzaffarnagar, UP, India from March 2020 to March 2022.

Results: A total of 150 subjects were enrolled in this study. 75 subjects were taken Calcium Dobesilate drug (500mg) twice a day for 08 weeks and 75 were taken Placebo Drug. 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.

Conclusion: Calcium Dobesilate improves the symptoms of objectively diagnosed CVI, independent of the concomitant usage of compression stockings.

Keywords: Calcium Dobesilate, Chronic Venous Insufficiency (CVI)

Introduction

Chronic venous insufficiency (CVI) is known to cause discomfort to the patients and might hamper with day-to-day activities. Patients with varicose veins and the complications of chronic venous ulceration is estimated to consume a 2-3% of the health budget in western countries [1]. The point prevalence of venous disease may be as high as 50% [2, 3]. CVI is caused due to alterations in the venous wall along with valvular incompetence, leading to hemodynamic changes within the lower limbs. Additionally, high pressures in the lower limb distend the veins

and separate the valves, making it incapable of preventing the back flow of blood and resulting in venous stasis and dilatation which in turn leads to an increase in micro-circulatory disorders [4].

The assessment and treatment of the severity of venous disease may be classified sing the CEAP (clinical, etiologic, anatomic, patho-physiological) system [5]. Clinically, patients with venous insufficiency usually complain of a pain in leg, and on examination increased leg diameter, edema, are found along with the presence of other associated clinical symptoms such as cramps, swelling, heavy legs, paresthesia, restless legs[6,7].

The mainstay of treatment is the correction of superficial venous reflux which is done mainly by traditional vein surgery, endothermal ablation or foam sclerotherapy and compression stockings. However, stockings may be difficult to put on and uncomfortable to wear and patients are often unwilling to undergo surgical intervention, particularly elderly patients with venous ulceration [8].

Moreover, even after surgical treatment some patients might complain of the similar symptom. Systemic drug therapy has been tried for many years in an attempt to reduce symptoms due to varicose veins and pharmacologically sought to reduce the chronic skin sequelae due to venous hypertension.

Calcium dobesilate is a vaso-active drug with effects on endothelial integrity, capillary permeability and blood viscosity. It is often recommended for venous disorders, and also prescribed for diabetic retinopathy and other microvascular disorders [4]. In addition, it also exerts its therapeutic effect in microcirculatory disorders by reducing capillary permeability, inhibiting platelet aggregation and thrombus formation, lowering blood hyper viscosity, and increasing red cell flexibility and also improves lymphatic drainage, which contributes to its anti-edematous effect [4].

In this study we compare the efficacy of calcium dobesilate versus placebo for chronic venous insufficiency**.**

Materials and method

This prospective study was carried out in Department of Surgery, Muzaffarnagar Medical College,Muzaffarnagar, UP, India. A total of 150 patients who presented to surgery OPD between March 2020 to March 2022 in Muzaffarnagar Medical college for treatment of Chronic venous insufficiency were studied according to risk factors, cause along with before and after administration of calcium dobesilate and placebo drug.

The selected patients were divided into 2 groups –

Group A: Receiving Calcium Dobesilate

Group B: Receiving Placebo Drug

Inclusion Criteria

In this study, the Patient having chronic venous etiology, were included.

Patients with Telangectasia or reticular veins, patient having edema of feet/ankle, Varicose veins, Skin pigmentation and / or eczema, Lipodermatosclerosis and/or atrophie blanche, Healed venous ulceration, Active venous ulceration, Patient giving consent , Age > 20 year and < 70 year and Pregnant Female were included in this study.

Exclusion Criteria

All those patients who presented with symptoms of deep vein thrombosis, patients who want to undergo elective surgery for varicose veins and varicose ulcer, patients less than 20 years and more than 70 years of age, patients with similar complaints in past and patient not giving consent were excluded from the study.

This study comprised of 150 patients who were studied prospectively according to risk factor, venous disability score, symptoms, age, body mass index and type of treatment received after which they were divided in 2 groups as follows –

GROUP A: Calcium Dobesilate 500 mg given twice daily for 8 weeks (N=75)

GROUP B: Placebo drug (N=75)

A detailed history and clinical examination was done to find out patients of chronic venous insufficiency. The clinical parameters were graded(0-4;0,absent;1,mild;2,moderate;3,severe;4, very severe) both before and after therapy. The clinical parameters were Pain, Itching, Tiredness, Heaviness, Paresthesia, Cramps and leg swelling.

Color Doppler was done in all cases to confirm the diagnosis of varicose veins, determine the competence of the valves, and to rule out deep vein thrombosis. Routine investigations along with urine examination were performed both before and after treatment.

Statistical Analysis:

Results were analyzed using Chi Square test, Student's t-test and Fisher'stest. Significant values were noted in both the groups. During follow up period, the patient was followed up for recurrence and worsening of symptom upto 6 months.

Results

Our study enrolled 150 patients who were divided into 2 groups according to the treatment received. Mean age of the patients in Group A was 52.23 year with that of Group B being 53.32 years. Venous disability score grading for both the groups were done before receiving the therapy which is shown in the table 1 as follows. The most common risk factor was prolonged standing followed by obesity and pregnancy as shown in table 2.

Calcium dobesilate when given to patients of chronic venous insufficiency presenting with the symptoms showed decrease in pain, venous edema, varicose vein and use of compression therapy as compared to placebo drug (table 3 and 4).

Table No.1 Showing demographic and Venous disability score in studied subjects.

Variables	**Group –A**	**Group –B**	**P-Value**
No. of Patients	75	75	
Male	32	40	0.1
Female	43	35	
Mean Age	52.23	53.32	0.8
Mean BMI	27.43	28.32	0.001*
Venous Disability Score			
Asymptomatic	6	3	0.3
Symptomatic but to Carries out activities without Compressive Therapy	10	12	0.6
Carries out activities without Compressive Therapy	65	72	0.04*
Unable to carry out Activity	10	20	0.04*

*Statistically Significant ($p<0.05$)

Table No.2: Showing comparison of risk factors in studied subjects.

Risk Factor	**Group-A**	**Group-B**	**p-Value**
Prolonged standing	52	39	0.02*
Immobilization	8	12	0.33
Raised intra-abdominal pressure	14	20	0.24
Pregnancy	4	12	0.03*
Chronic constipation	31	50	0.06
Tight clothes	22	43	0.1
Obesity	32	45	0.03*

*Statistically Significant ($p<0.05$)

Table No. 3: Showing Comparison of Use of Calcium dobesilate and Placebo in studied subjects

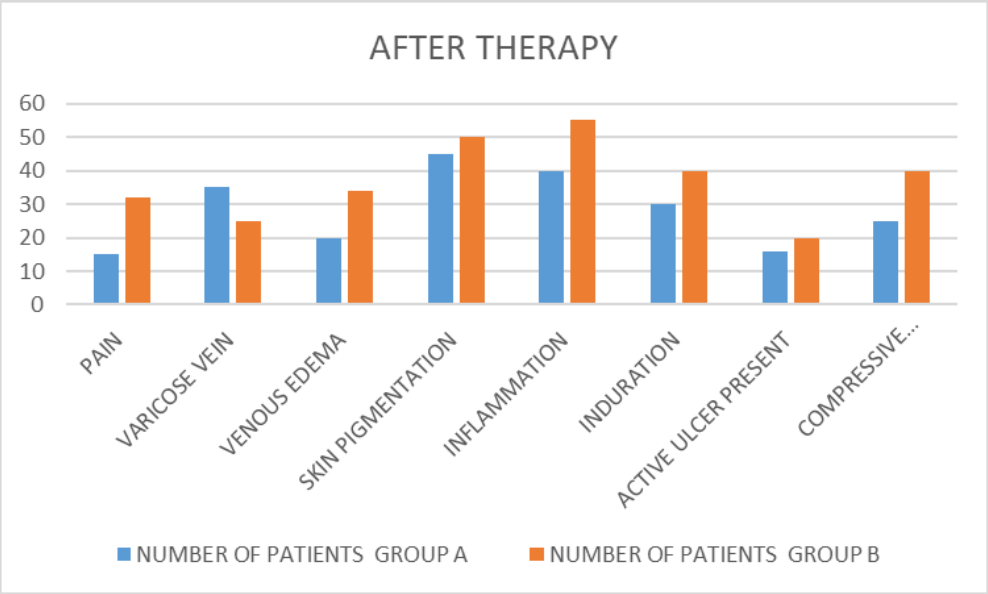
Variable	**Group A (N=75)**	**Mean Severity Score**	**Group B (N=75)**	**Mean Severity Score**
Pain	55	2	46	2
Varicose Veins	45	2	50	3
Venous Edema	50	3	44	2
Skin Pigmentation	55	2	59	3
Inflammation	69	2	72	2
Induration	45	2	55	2
Active ulcer present	22	1	27	2
Compressive therapy used	65	3	72	2

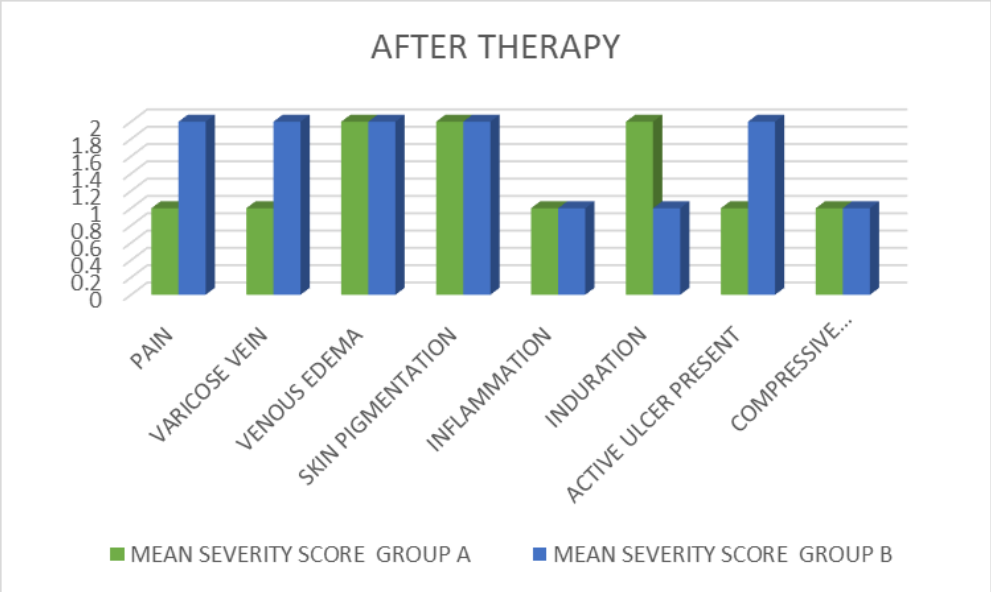
Table No.4 Showing Comparison of Calcium dobesilate and Placebo in studied subjects

Variable	**Group- A (N=75)**	**Mean Severity Score**	**Group- B (N=75)**	**Mean Severity Score**	**P -Value**
Pain	15	1	32	2	0.0002*
Varicose Vein	35	1	25	2	0.005*
Venous Edema	20	2	34	2	0.0002*

Skin Pigmentation	45	2	50	2	0.6
Inflammation	40	1	55	1	0.08
Induration	30	2	40	1	0.5
Active Ulcer Present	16	1	20	2	0.9
Compressive Therapy Used	25	1	40	1	0.017*

*Statistically Significant ($p<0.05$)





Discussion

Chronic venous insufficiency (CVI) mainly refers to the lower extremity edema, skin changes, and mostly discomfort secondary to venous hypertension. This is a prevalent disease which if left untreated usually progresses

and leads to the DVT and venous ulcers. The patient may complain of pain, swelling, skin discoloration along with cosmes is defect.

In our study we compared the efficacy and effectiveness of calcium dobesilate with the placebo drug to which we inferred that calcium dobesilate reduces pain, venous edema, varicose veins and use of compressive therapy to a significant rate with reduction of severity score from 3 to 1.Moreover, it had no effect on reduction of inflammation, skin discoloration, active ulcer reduction but still this medication can be used as a primary treatment in reduction of the symptoms.

A study by Angehrn F et al [9] was designed to evaluate the efficacy and safety of calcium dobesilate in a large population of ambulatory patients with overt chronic venous insufficiency. 373 patients (age range, 20 to 76 years) were treated for 28 days with 1.5 g calcium dobesilate per day. The results showed a significant reduction of ankle and calf edemas, corresponding to 4.4% and 2.8% of the respective initial circumferences and representing a reduced volume of 0.13 L, was noted in more than 82% of patients at the outcome compared with baseline conditions in turn showing that calcium dobesilate is effective.

Ciapponietal(10) report a meta-analysis of the effectiveness and safety of calcium dobesilatein CVI in ten RCTs (778 patients), calcium dobesilate was compared with placebo in the treatment of CVI. Calcium dobesilate significantly improved night cramps and discomfort nearly twice as well as placebo.

Another RCT by Danielsson G et al [11] compared MPFF with placebo and could only show a difference in night cramps without changing other symptoms of CVD. A recent large RCT by Gohel MS et al [12] with 509 patients could not show a difference between its study groups.

However, a double blind, placebo-controlled trial by Rabe E et al [13] showed that calcium dobesilate reduces legoedema and improves the symptoms of objectively diagnosed CVD independent of the concomitant usage of compression stockings.

A study by Koltringer et al [14] tried to separate the apparent viscosity of whole blood, which includes both its elastic and viscous properties, into these two components and then to study them separately for alterations so as to assess the effects of the test compound more accurately. For this purpose, 50 patients with impaired peripheral blood flow were selected and studied.

Of the randomly recruited patient sample, 33subjects suffered from cerebro-vascular insufficiency, the remaining 17 suffered from impaired peripheral arterial blood flow stage IIa according to Fontaine. All patients were given 500 mg calcium dobesilate three times daily for a period of two weeks. They had not received any active medication. Before the start of the study and at 14 days, visco-elasticity of whole blood and plasma as well hematocrit and microcirculation were measured. All viscosity and elasticity values fell in a highly significant manner, with plasma viscosity showing the greatest variation. In addition to the decrease in visco-elasticity, hematocrit also showed a highly significant decrease.

Conclusion:

Calcium dobesilate is an effect drug which can be given as a primary treatment for chronic venous insufficiency.

References

1. Van den Oever R, Hepp B, Debbaut B, Simon I. Socio-economic impact of chronic venous insufficiency. An under estimated public health problem. Int Angiol 1998;17:161-7.

2. Carpentier PH, Maricq HR, Biro C, Poncot-Makinen CO, Franco A. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: apopulation-based study in France. JVascSurg 2004;40:650-9.

3. FowkesFG, EvansCJ, LeeAJ. Prevalence and risk factors of chronic venous insufficiency. Angiology 2001;52 Suppl1:S5-15.

4. AkgunOO, ArslanC, SuzerO, BozkurtAK: The effects of calcium dobesilate and micronized purified flavonoid fractions on myocardial protection. Turkish J Thorac Cardiovasc Surg, 2011;19:417–24

5. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. JVascSurg 2004;40:1248-52.

6. Bradbury AW, Evans CJ, Allan PL, Lee AJ, Ruckley CV, Fowkes FG. Vascular surgical society of Great Britain and Ireland: symptoms of varicose veins. BrJ Surg1999;86:700.

7. Langer RD, Ho E, Denenberg JO, Fronek A, Allison M, Criqui MH. Relationships between symptoms and venous disease: the San Diego population study.Arch Intern Med 2005;165:1420-4.

8. GohelMS, BarwellJR, Taylor M, Chant T, FoyC, Earnshaw JJ, etal. Long term results of compression therapy alone vs. compression plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. BMJ2007;335:83.

9. Angehrn F. Efficacy and safety of calcium dobesilate in patients with chronic venous insufficiency: Anopen-label, multicenter study. Current Therapeutic Research 1995;56(4) 346-56.

10. Ciapponi A, Laffaire E, Roque M. Calcium dobesilate for chronic venous insufficiency: asystematic review. Angiology2004;55(2):147-54

11. Danielsson G, Jungbeck C, Peterson K, Norgren L. A randomized controlled trial of micronized purified flavonoid fraction vs placebo in patients with chronic venous disease. Eur J Vasc Endovasc Surg2002; 23:73e6.

12. GohelMS, DaviesAH. Pharmacological agents in the treatment of venous disease: an update of the available evidence. Curr Vasc Pharmacol 2009; 7:303e8.

13. RabeE, Jaeger KA, Bulitta M, Pannier F. Calcium dobesilate inpatients suffering from chronic venous insufficiency: a double-blind, placebo-controlled, clinical trial.Phlebology2011; 26:162e8.

14. Koltringer P, Esber O, Rothlauer W, Klima G, Lind P, Langsteger W, Waonig P. Calcium dobesilate and its effects on hemorheology and microcirculation. Int J Clin Pharmacol Ther Toxicol 1988;26 (10):500-02.