Calcium Dobesilate – Calcium 2,5 dihydroxybenzene is a synthetic compound with Angioprotective Action through several steps in the pathophysiology of vascular diseases. It exerts its therapeutic effect in microcirculatory disorders by reducing capillary permeability, improving lymphatic drainage, inhibiting platelet aggregation and thrombus formation, lowering blood hyperviscosity and increasing red cell flexibility\(^1,2\).

Calcium Dobesilate has demonstrated to produce significant improvement in the management of varicose veins, chronic venous insufficiency, hemorrhoids and diabetic retinal angiopathy\(^3\).

**Calcium Dobesilate is a Capillotropic, Venotropic and Vasculoprotective Agent**

**A Multi- Faceted Mechanism of Action**\(^1,4\)

- **Restores Endothelial Structure & Function**
  - Enhances Nitric Oxide (NO) Production

- **Vasculoprotective Action**
  - Scavenges Oxygen Free Radicals
    - Decrease in Oxidative Stress
    - Decrease Platelet Activity Factor
    - Lipid Peroxidation
  - Inhibits Vasoactive Actions of Histamine and Bradykinin
  - Inhibits Platelet Aggregation as well as Thrombus Formation in the Microcirculation

- **Decreases Capillary Permeability & Hyperpermeability**

- **Stimulates Proteolysis by Macrophages**

- **Lymphotropic Action (improves lymphatic drainage)**

- **Relaxation of Blood Vessels and Restores Blood Flow**

- **Decreases Edema**

- **Lowers Blood Viscosity**

- **Restores Tissue Perfusion**

- **Improves Erythrocyte Function**

- **Improves microangiopathy**
Efficacy of Calcium Dobesilate in Management of Acute Attacks of Hemorrhoidal Diseases

Hemorrhoidal disease is currently believed to be caused by distal displacement and structural distortion of anal cushions, which are physiologic structures with an important role in defecation and continence. Anatomic studies have revealed that the anchoring and supporting epithelial tissues deteriorates with ageing, and the descended loose lining becomes more sensitive to pressure from straining and trauma from stool, resulting in venous distension, inflammation, erosion, bleeding and/or thrombosis. Controversies still exists and there is lack of agreement on the treatment strategies. Radical approaches to eliminate hemorrhoids involve surgical excision or invasive endoscopic interventions called mucosal fixation methods, such as band ligation or injection sclerotherapy, which depend on inflammation and subsequent scarring causing attachment to underlying muscle.

A more conservative policy is based on the current data that hemorrhoids are normal anatomic structures, and age related structural changes occur in every person, where as symptoms develop in some people. Therefore, hemorrhoidal disease is believed to be a purely clinical condition with chronic symptoms interspersed with recurrent, self-resolving acute episodes, and symptomatic treatment together with preventive measures might be all that is needed to be done.

Calcium dobesilate’s beneficial effects are related to its ability to decrease capillary permeability, platelet aggregation and increase lymphatic transport. Because these properties reasonably contribute to the acute inflammatory attacks of hemorrhoidal disease, This compound has promising effect on the acute symptoms of hemorrhoids.

Mentes BB and co-workers conducted a randomized, double blind, controlled study to investigate the efficacy and of oral calcium dobesilate therapy for two weeks in treating 45 patients with acute attacks of first- and second- degree internal hemorrhoids. Twenty patients were administered the study drug, where as 16 patients received only high fiber diet to serve as control. Both symptoms and anoscopic scores before and after therapy were compared.

A success rate of 86.21% with cessation of bleeding plus lack of severe anitis anoscopically at two weeks were achieved with calcium dobesilate. The improvement in the percentage of symptoms and anitis score is presented in Table 1.

Table 1: The Frequencies and Percentages of the Symptom and Anitis Score of the Control (Diet) and Study (Calcium Dobesilate) Groups before and after Treatment

<table>
<thead>
<tr>
<th>Symptom Score before treatment</th>
<th>Control diet (n=16)</th>
<th>Calcium Dobesilate (n=29)</th>
<th>Anitis Score before treatment</th>
<th>Control diet (n=16)</th>
<th>Calcium Dobesilate (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1</td>
<td>—</td>
<td>16 (100%)</td>
<td>1</td>
<td>6 (37.5%)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>2</td>
<td>16 (100%)</td>
<td>29 (100%)</td>
<td>2</td>
<td>10 (62.5%)</td>
<td>20 (69%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom Score after treatment</th>
<th>Control diet (n=16)</th>
<th>Calcium Dobesilate (n=29)</th>
<th>Anitis Score after treatment</th>
<th>Control diet (n=16)</th>
<th>Calcium Dobesilate (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4 (25%)</td>
<td>20 (69%)</td>
<td>0</td>
<td>2 (12.5%)</td>
<td>15 (51.7%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (18.8%)</td>
<td>6 (20.7%)</td>
<td>1</td>
<td>7 (43.8%)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>2</td>
<td>9 (56.3%)</td>
<td>3 (10.3%)</td>
<td>2</td>
<td>7 (43.8%)</td>
<td>2 (6.9%)</td>
</tr>
</tbody>
</table>

Symptom Score: 0=signtific relief or lack of any symptoms; 1= partial relief of symptoms - minor complaints with no bleeding; or 2= no relief or worsening (bad) and/or persistent bleeding.

Anitis Score: 0= no signs of hemorrhoidal disease or a pink, healthy mucosa without any signs of inflammation; 1= a rather inactive grade 2 hemorrhoid without overt inflammatory findings (mild anitis); or 2= an actively or easily bleeding hemorrhoid with overt signs of inflammation and edema (severe anitis)

An important feature of this study is that the treatment outcome was not based upon only on symptoms, but also on objective criteria. A significant improvement afforded by this agent in the anoscopically observed inflammation deserves emphasis. Both the symptom and objective inflammation scores were significantly better then those of the control- diet group.
VARICOSE VEINS, VENOUS ULCERS, VARICOSE ULCERS – PROMISING ROLE OF CALCIUM DOBESILATE

Varicose veins and their accompanying secondary complications, namely venous ulcers and stasis dermatitis are associated with chronic morbidity, economic loss and reduction in the patient’s quality of life. Venous ulcers constitute the majority of leg ulcers, accounting for up to 80%. The overall prevalence of venous ulcers in the general population is in the range of 2%. Stasis dermatitis commonly accompanies venous ulcers and is severely disabling to treat. Venous ulcers incur substantial costs. In Europe, they account for 1-2% of their healthcare budget. The annual cost of treatment is $1 million in Sweden and $1.9-2.5 billion in USA. Thus there has been a renewal of interest in the development of new medical measures for the management of such conditions, as venous ulcers do not require surgical intervention as often as arterial ulcers.

Calcium dobesilate is very effective in the conditions of chronic venous insufficiency (CVI), otherwise known as “heavy leg syndrome” or venous varicosities. It acts at various levels of the disease process as shown in Figure 1.

In a double blind trial of the drug used at a dose of 500mg twice daily for a period of 6 weeks in 30 normal subjects and 30 patients with chronic venous insufficiency, there were no significant alterations in the normal subjects; the active drug produced significant improvements (P<0.05) in most symptoms, including feelings of heaviness, swelling, tiredness, and aching in the lower extremities. Hachen and Lorenz, in a similar placebo-controlled trial of 500mg of calcium dobesilate twice daily for 6 weeks, reported highly significant improvement in Plethysmographic and clinical parameters, including the sensation of heaviness and malleolar edema, and a lesser effect on the painful sensations of tension and pressure.

Arceo A and group enrolled three hundred fifty-two patients with CVI in grades I and II of Widmer’s classification from an open population between January 1999 and June 2000; patients received calcium dobesilate 500mg every 8 hrs for 9 weeks. A basal recording every 3 weeks were made of heaviness, pain, cramps and paresthesias of the lower limbs with a severity scale and edema was assessed by measurement of the circumference of ankles and calves. Two hundred eighty-six patients (81.3%) were women and 66 (18.7%) were men with a mean age of 45.7 ± 14.1 years; 200 patients (56.8%) were grade I and 150 (42.6%) were grade II of Widmer’s classification and two patients had no classification with a mean duration of symptoms of 6.5 ± 7.4 years. Significant improvement was observed in all the symptoms as shown in Figure 2. In regard to edema of ankles and calves, a significant reduction in circumferences was registered in both sites at the end of treatment.

Figure 1: Pathogenesis of Venous Ulcer and Sites of Action of Calcium Dobesilate (as cross marks).
Chandandeep K et al. in their pilot study enrolling 25 patients with venous ulcer and stasis dermatitis, reported significant post-therapeutic improvement in the clinical symptoms of pain, itching, tiredness, heaviness, paresthesia and leg swelling (as presented in Table 2). Color Doppler studies showed significant improvement in valvular competence. A remarkable decrease in the leg ulcer areas, as well as a subjective improvement in oozing and tenderness, after treatment with calcium dobesilate. All of these observations indicate microcirculatory improvement in the patients. The observations from these studies demonstrated that calcium dobesilate is an effective therapy, with no undesirable side-effects. It is very well-suited for long term use in the treatment of stasis ulcer and dermatitis and if the drug is started at an early phase of the disease process, morbidity could be prevented.

Table 2: Improvement in Clinical Symptoms, leg ulcer area and Parameters of Dermatitis after Calcium Dobesilate Therapy

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Before Therapy (Mean ± SD)</th>
<th>After Therapy (Mean ± SD)</th>
<th>P value* (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>3.78 ± 0.42</td>
<td>0.39 ± 0.50</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Itching</td>
<td>3.55 ± 0.51</td>
<td>0.45 ± 0.51</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Tiredness</td>
<td>3.82 ± 0.39</td>
<td>0.32 ± 0.46</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Heaviness</td>
<td>3.74 ± 0.45</td>
<td>0.65 ± 0.57</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3.80 ± 0.44</td>
<td>1.20 ± 1.64</td>
<td>P &lt; 0.06</td>
</tr>
<tr>
<td>Cramps</td>
<td>3.92 ± 0.27</td>
<td>0.61 ± 0.65</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>3.89 ± 0.31</td>
<td>0.63 ± 0.68</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mean leg ulcer area (cm²)</td>
<td>9.82 ± 17.89</td>
<td>1.35 ± 3.61</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Stasis dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>3.55 ± 0.51</td>
<td>0.45 ± 0.51</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Oozing</td>
<td>3.65 ± 0.55</td>
<td>3.04 ± 0.70</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

*P < 0.05 is the accepted significance value

**CALCIUM DOBESILATE – NEWER PERSPECTIVES IN DIABETIC RETINOPATHY**

Diabetic retinopathy (DR), is among the most feared microvascular complications of diabetes. In type 2 diabetes of 15 or more years duration the risk of retinopathy is approximately 80% [13]. The major vision-threatening complications include macular oedema, macular ischaemia, and neovascularisation with pre-retinal or vitreous haemorrhage, retinal detachment and neovascular glaucoma.

Their initial stage begins with abnormal fragile blood vessels, hyperpermeability of retinal capillaries, desquamation and endothelial dysfunction and basal membrane thickening. Though the pathogenetic mechanisms of Diabetic Retinopathy is yet to be understood completely, hyperglycemia related changes in biochemical processes are clearly evident, that may result in anatomical and functional changes in the retinal vasculature. The crucial role of blood hyperviscosity combined with alteration in blood rheology provides good evidence to the etiology of diabetic retinopathy [14].
Published clinical studies on patients with DR and treated with Calcium Dobesilate were evaluated (Table-3) and selected for a meta-analysis as listed in a medical documentation retrieval system. The efficacy variable retained in four double-blind studies was blood viscosity. In three studies, permeability was evaluated: haemorrhage area, capillary fragility and the fluorescein penetration ratio in the vitreous humor. Blood fibrinogen levels and visual acuity were also recorded.15-20.

### Table 3: Clinical Studies of Calcium Dobesilate in Diabetic Retinopathy (and/or Glaucoma)

<table>
<thead>
<tr>
<th>Ref</th>
<th>First author</th>
<th>Methodology</th>
<th>Outcome</th>
<th>Patients (number)</th>
<th>Dose regimen (mg/day)</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Larsen et al</td>
<td>Double-blind Cross-over</td>
<td>Skin capillary resistance</td>
<td>18</td>
<td>750</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td>Vojnikovic et al</td>
<td>Double-blind</td>
<td>Blood viscosity and aqueous humor, visual acuity</td>
<td>50</td>
<td>1500</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>Salama et al</td>
<td>Double-blind</td>
<td>Blood viscosity</td>
<td>37</td>
<td>1500</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>Vinazzer et al</td>
<td>Double-blind</td>
<td>Blood viscosity, Visual acuity</td>
<td>20</td>
<td>1500</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>Vojnikovic et al</td>
<td>Double-blind</td>
<td>Blood viscosity and intra-ocular pressure</td>
<td>79</td>
<td>1500</td>
<td>6</td>
</tr>
</tbody>
</table>

There is now good evidence that blood viscosity may contribute to the development of microcirculatory lesions in the diabetics. The importance of blood viscosity, platelet aggregation in the etiology of diabetic retinopathy has been well accepted due to efforts of many investigators in the field of hemorrheology.18,21. The crucial role of viscosity is apparent in the microcirculation, and noticeable in retina, due to abnormal blood rheology combined with alterations in the structure of the small vessels.

It is clear that Calcium Dobesilate lowers the hazards of endothelial cell dysfunction which contributes to the microangiopathy. The pharmacological results in vitro, in animal models are in line with the findings in clinical trials, which also includes increase capillary fragility in diabetic patients can be normalized by Calcium Dobesilate (capillary strengthening effect).19. This, in turn, explains the beneficial results obtained in diabetic retinopathy, namely decreased vascular permeability, blood viscosity, fibrinogen levels and improved visual acuity.

### Calcium Dobesilate - Role in Glaucoma

The principal factor in the pathogenesis of glaucomatous optic nerve damage is interference with axoplasmic blood flow (i.e., the movement of cytoplasmic material, axoplasm along the axon of a nerve). The interference might be mechanical or vascular depending on whether it is a direct compression or insufficiency in blood flow. The debate in the pathogenesis acquired a new dimension with the appearance of blood viscosity as an important risk factor of glaucoma. When a group of patients with diabetic retinopathy and blood hyperviscosity, and also had open-angle glaucoma was treated with Calcium Dobesilate, the resultant fall in the blood viscosity was not only associated with the expected improvement in diabetic retinopathy, but also with a fall in intraocular pressure and improvement in glaucomatous visual fields.

An association between glaucoma and diabetes is well known, and it has been reported that the prevalence of glaucoma in a diabetic population is about 3 times greater than that found in non-diabetics of the same age. Calcium dobesilate as an angio-protective agent in addition to its lowering blood, plasma and aqueous humor hyperviscosity, reduces microvascular hypermeability, possess platelet anti-aggregatory activity. Therefore the effect is mediated through a multi-directed action.

In a double-blind randomized study, 79 non-insulin-dependent subjects with early retinopathy and open angle...
glaucoma received either three 500mg Calcium Dobesilate or placebo for six months. At the end of the study, statistically significant differences in the drug group compared with the placebo group were recorded: intraocular pressure (Table 4), visual field defects, surface area of retinal hemorrhages, and whole blood and plasma viscosity were reduced significantly²⁰.

Table 4: Reduction in Intraocular Pressure (IOP) in patients with D R and G laucoma, when treated with Calcium Dobesilate or Placebo. (n= 79).

<table>
<thead>
<tr>
<th>Treatment Gr</th>
<th>IOP (mm of Hg ; mean ± SD)</th>
<th>Before Rx</th>
<th>After 3 months of Rx</th>
<th>After 6 months of Rx</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Dobesilate</td>
<td>26.20 ± 3.22</td>
<td>21.83 ± 2.84</td>
<td>19.80 ± 1.70</td>
<td>P&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>26.24 ± 2.68</td>
<td>25.74 ± 2.85</td>
<td>25.55 ± 1.75</td>
<td>Not significant</td>
<td></td>
</tr>
</tbody>
</table>

The therapeutic effects are due to its multi-pronged actions. By diminishing capillary permeability, and stabilizing alterations in the blood-retinal barrier, treatment with Calcium Dobesilate leads to a reduction in the extravasations of blood from the retinal vessels and to the maintenance of normal hemodilution. Further, by lowering elevated levels of large plasma protein and diminishing erythrocyte hyprrigidity and hyper-aggregability. Calcium dobesilate also improves the flow properties of blood and by reducing platelet hyperaggregation, it inhibits ischemia²⁰.

**SUMMARY**

Calcium dobesilate is a capillotropic, venotonic and vasculoprotective agent. It provides clinical improvements in various vascular diseases by its action on the microcirculation, both at the capillary level and at the hemorrheologic level. As an effective therapy with minimal side effects, it is suitable for long-term use in the treatment of stasis ulcers and dermatitis.

Calcium dobesilate supplemented with high fiber diet provide considerable symptomatic and objective improvement in patients suffering from acute attacks of internal hemorrhoids. Thus decreasing the pain and discomfort of the disorders.

Calcium dobesilate with its “rheology activity” at multiple steps, is highly effective in Diabetic Retinopathy and glaucoma and provides beneficial results in terms of decreased vascular permeability, blood viscosity, fibronogen levels and improved visual acuity.

**REFERENCES**

DOBEST
(CALCIUM DOBESILATE)

Diabetic Retinopathy
Glaucoma
Chronic Venous Insufficiency
Venous Ulcer
Diabetic Microangiopathy
Haemorrhoids

Helps Patients Do their BEST

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