

Efficacy of Calcium Dobesilate in Treating Acute Attacks of Hemorrhoidal Disease

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PURPOSE: A randomized, double-blind, controlled study was conducted to investigate the efficacy of oral calcium dobesilate therapy in treating acute attacks of internal hemorrhoids. **METHODS:** Twenty-nine well-documented adult patients with first- or second-degree internal hemorrhoids were treated with calcium dobesilate for two weeks, while 16 patients received only a high-fiber diet to serve as control. Both symptoms and anoscopic inflammation were scored on a scale from 0 to 2 before (T_0) and two weeks after treatment (T_2). **RESULTS:** A success rate of 86.21 percent with cessation of bleeding plus lack of severe anitis anoscopically at two weeks were achieved with calcium dobesilate. The pretreatment symptom score of 2 fell significantly to 0.45 ± 0.13 , and the pretreatment anitis score of 1.69 ± 0.09 fell to 0.55 ± 0.12 at T_2 ($P = 0.0001$ for both comparisons). The symptom and anoscopic inflammation scores obtained with calcium dobesilate treatment were also significantly better than those with diet only ($P = 0.0017$ and $P = 0.0013$, respectively). **CONCLUSION:** Together with recommendations about diet and bowel discipline, oral calcium dobesilate treatment provides an efficient, fast, and safe symptomatic relief from acute symptoms of hemorrhoidal disease. This symptomatic healing is associated with a significant improvement in the anoscopically observed inflammation. [Key words: Hemorrhoidal disease; Calcium dobesilate]

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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.^{1, 2} According to some western population statistics, the prevalence is surprisingly high, with an equal frequency in men and women.^{3, 4} Anatomic studies have revealed that the anchoring and supporting subepithelial tissue deteriorates with aging, and the descended loose lining becomes more sensitive to pressure from straining and trauma from stool, occasionally resulting in venous distention, inflammation, erosion, bleeding, and/or thrombosis.^{2, 5} Regarding

the more common form of internal hemorrhoids, the most common symptom is the passing of bright red blood at stool. Discomfort, pruritus, soiling, pain, and/or protrusion may also be encountered, especially in advanced or complicated cases. Patients with first-degree (1°) or 2° internal hemorrhoids lack advanced prolapse of the supporting subepithelial tissue of hemorrhoidal cushions. Nevertheless, these patients may experience acute attacks with severe discomfort and bleeding.^{2, 6, 7} Especially young men with a tight anal canal can have severe discomfort and severe bleeding during acute attacks, with the minimal visible abnormality of 1° internal hemorrhoids.⁷ The finding of proctoscopic "anitis," which correlates with enlarged lamina propria capillaries with inflammation, is associated with the occurrence of typical hemorrhoidal bleeding and/or pain.^{2, 7, 8} The increasing extent of prolapse defines increasing degrees (2°, 3°, and 4° hemorrhoids), although it is not always directly correlated to the severity of signs or symptoms.

There still exist controversies and lack of agreement on 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.^{6, 9} 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, whereas symptoms develop in only some people.^{2, 5} 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 needs to be done.^{5, 10}

Calcium dobesilate (calcium 2,5-dihydroxybenzenesulfonate) is a drug with previously demonstrated

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efficacy in the treatment of diabetic retinopathy and chronic venous insufficiency.¹¹⁻¹³ These beneficial effects of the drug are related to its ability to decrease capillary permeability, platelet aggregation, and blood viscosity and to increase lymphatic transport.¹⁴ Because these properties would reasonably be expected to contribute to the acute inflammatory attacks of hemorrhoidal disease, this randomized, double-blind, controlled study was conducted to investigate the efficacy of calcium dobesilate in treating acute attacks of hemorrhoidal disease, based on objective healing and subjective/symptomatic criteria.

PATIENTS AND METHODS

Patient Selection and the Study Design

A total of 45 adult patients with first- (1°) or second-degree (2°) internal hemorrhoids are reported. In all patients, intermittent symptoms attributable to hemorrhoids had existed for longer than six months (range, 6 months to 8 years; median 24 months) and rectal bleeding was currently present, indicating an acute attack. Patients with 3° or 4° hemorrhoids, in whom the prolapse needed manual reduction or was not reducible, were excluded. Other exclusion criteria were concurrent fistula or chronic anal fissure, inflammatory bowel disease, diabetes or other metabolic/endocrine disorders, alcoholism, drug abuse, coagulation disorders, abnormal sexual habits, previous anorectal surgery, or previous treatment of the hemorrhoidal disease with any method other than diet modification and/or topical agents. Rectosigmoidoscopy and barium enema (if indicated) were included in the workup to rule out any associated colorectal cause of symptoms. Ethical approval was obtained from the University Ethical Committee. After the initial anoscopic evaluation at entry (T_0), the patients were randomly assigned by simple random sampling using the random table to enter the study or the control group. Because of the unsatisfactory results obtained in the control group (details below), randomization was stopped when the number of the control patients reached 16 (instead of 30), but the study group was continued with the consecutive appropriate patients.

Group 1 (control-diet group, n = 16): Only diet manipulation and other conservative measures (details below) were applied.

Group 2 (study-Doxium® group, n = 30): After the initial anoscopic evaluation, a loading dose of Doxium® (OM Laboratories, Geneva, Switzerland;

three tablets per day in three divided doses) was given initially for seven days and followed by two tablets daily (one tablet *b.i.d.*) for another week. The patients also received dietary and lifestyle advice, as did patients in the control group.

Diet Manipulation

A high-fiber diet, prepared by the diet unit, was explained to all patients in both groups, and the intake of nonstarch polysaccharides was aimed to exceed 20 g/day.¹⁵ Strict obedience was not pursued, but the patients were informed about the importance of fiber in healthy nutrition and encouraged to consume fruit, vegetables, and whole grain bread. Frequent alcohol intake and regular heavy consumption of spices were also prohibited.

Furthermore, encouragement was given to correct other general causes of constipation and unhealthy defecation habits, such as ignoring the need to pass stools, irregular meals, spending a long time in the lavatory, straining, and lack of exercise. To aid their memory, we give our patients a printed list of instructions about the high-fiber diet and defecation habits.

Patient Follow-up and Evaluation of Healing. The patients were interviewed/re-examined by a blinded investigator on Days 7, 14, and then on every two months. If symptomatic relief was achieved, the day of relief from symptoms (with regard to T_0) was recorded. The baseline symptomatic score at T_0 was regarded as 2, and the symptoms were noted on follow-up visits and scored as follows: 0 = significant relief or lack of any symptoms; 1 = partial relief of symptoms—minor complaints (better) with no bleeding; or 2 = no relief or worsening (bad) and/or persistent bleeding. Patients with more than one symptom were asked to evaluate them globally. A control anoscopy was performed on Day 14 (T_2), but further anoscopic evaluations were not intended on follow-up visits unless recurrent symptoms were noted. In addition to the symptoms, the degree of anitis on and around the hemorrhoids was evaluated at the initial (T_0) and control anoscopies (T_2) and scored by the same blinded investigators as follows: 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). For patients with more than one hemorrhoidal pack, the worst lesion

determined the outcome. If bleeding persisted, even to a lesser degree, for more than 14 days after the initiation of the diet or calcium dobesilate (symptom score 2) and/or severe anitis (anitis score 2) was noted anoscopically at T₂, this was regarded as treatment failure, and alternative treatment methods were applied (data not discussed). If mild anitis (anitis score 1) with cessation of bleeding was noted at T₂, calcium dobesilate (one tablet *b.i.d.*) was continued for two more weeks. The patients were encouraged to come immediately and not to wait for the next interview whenever they developed symptoms. Any recurrent bleeding was immediately evaluated by anoscopy plus colonoscopy and regarded as a recurrence of hemorrhoidal disease if another source was not detected by these investigations.

The Wilcoxon's paired-samples test and the Mann-Whitney *U* test were used for comparisons of the scores in and between groups, respectively. The success rates of the groups were compared with Fisher's exact chi-squared test. The scores were given as mean \pm standard error of the mean (SEM), and a *P* value of less than 0.05 was considered as significant.

RESULTS

Of the 16 patients in the control-diet group, 10 were male and the median age was 42 (range, 18–60) years. The age and gender distribution was similar in the Doxium[®] group, with 19 male patients and a median age of 43 (range, 19–59) years. One patient in this group was lost for follow-up, leaving 29 behind. All of the patients included in the study had current rectal bleeding. The presenting symptoms of the patients are documented in Table 1. All of the patients included had mild or severe anitis. The anitis scores of the control and Doxium[®] groups at T₀ were also comparable (1.63 ± 0.13 and 1.69 ± 0.09 , respectively; *P* = 0.66). Thirty-five patients (35/45, 77.8

percent) described irregular bowel habits and/or the frequent passage of hard stool.

Two weeks after the initiation of the diet, 86.7 percent (39/45) of the patients developed soft bulky stools and relatively regular bowel habits. With this improvement in bowel habits, a significant decrease in the symptom score of the diet group at T₂ (1.31 ± 0.22 ; *P* = 0.018) was noted. Of the 16 patients included in this group, 4 were symptom free and 3 declared partial relief. Nevertheless, 9 (56.25 percent) of the 16 patients still had rectal bleeding, and the anitis score at T₂ reached only marginal significance, compared with the initial anitis score (1.31 ± 0.18 at T₂ vs. 1.63 ± 0.13 at T₀, *P* = 0.0431). The results are shown in Table 2.

In the Doxium[®] group, cessation of bleeding plus lack of severe anitis anoscopically at T₂ were achieved in 25 of 29 cases, indicating a success rate of 86.21 percent within the time limits of this study (*P* = 0.0051, compared with the 43.75 percent success rate of the control group). Failure was determined in one patient because severe anitis was noted at T₂, although bleeding had ceased and partial symptomatic improvement was declared. The pretreatment symptom score of 2 fell significantly to 0.45 ± 0.13 at T₂ (*P* = 0.0001). This symptomatic healing was also significantly better than that achieved in the diet group (*P* = 0.0017). In the 25 successful cases, the time of significant relief from symptoms averaged 5.5 (range, 2–10) days. In parallel with the symptomatic healing, the posttreatment anoscopic anitis score (0.55 ± 0.12) was significantly better than the pretreatment anitis score (1.69 ± 0.09 ; *P* = 0.0001; Fig. 1), as well as the posttreatment anitis score of the control group (1.31 ± 0.18 ; *P* = 0.0013). The frequencies and percentages of the symptom and anitis scores of the control and Doxium[®] groups are shown in Table 3.

A single patient suffered from epigastric pain soon after the initiation of the drug. Endoscopic control revealed no specific abnormalities, and the pain subsided spontaneously despite ongoing treatment. Although no recurrent attacks have yet been noted, the follow-up period of the study group is short and ranges from 2 to 8 months.

DISCUSSION

The results of this study have shown that calcium dobesilate is highly effective in the treatment of acute attacks of hemorrhoidal disease. Twenty-five (86.21 percent) of 29 patients were noted to be symptom

Table 1.
The Presenting Symptoms of the 45 Patients Included in the Study

Presenting Symptom	No. of Patients (%)
Rectal bleeding	45 (100)
Anal pain	7 (15.6)
Anal pruritus	5 (11.1)
Mass feeling	3 (6.7)
Anal discomfort	10 (22.2)
Tenesmus	8 (17.8)
Constipation and/or irregular bowel habits	35 (77.8)

Table 2.
The Symptomatic and Objective Anitis (Anoscopic) Scores and the Success Rates of the Control (Diet) and Study (Doxium) Groups

Group	Symptom Score Before Treatment	Symptom Score After Treatment	Anitis Score Before Treatment	Anitis Score After Treatment	Success Rate (%)
Control-diet (n = 16)	2	1.31 ± 0.22*	1.63 ± 0.13	1.31 ± 0.22*	43.75
Doxium® group (n = 29)	2	0.45 ± 0.13†	1.69 ± 0.09	0.55 ± 0.12‡	86.20‡

* Significantly smaller than the pretreatment corresponding score ($P < 0.05$).

† Significantly smaller than the pretreatment scores ($P = 0.0001$) and the posttreatment corresponding score of the control group ($P < 0.01$) (see text for details of symptomatic and objective scoring systems).

‡ Significantly higher than the control group ($P = 0.0051$).

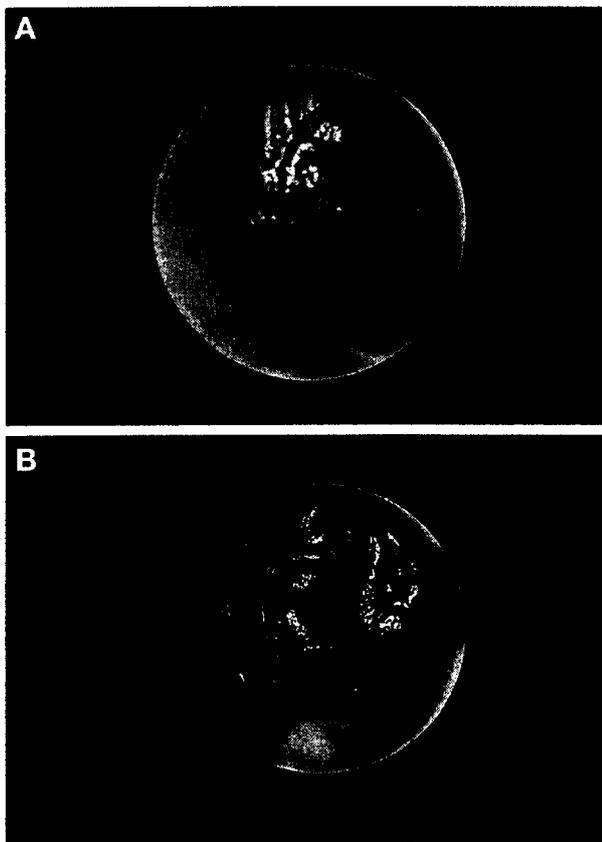


Figure 1. A. Anoscopic views showing severe anitis before treatment and complete healing. B. Healing of the inflammation in the same patient 14 days after treatment.

free or significantly improved with complete cessation of bleeding, as reflected by the significant difference between the symptom scores before and two weeks after treatment ($P = 0.0001$). An important feature of this study is that the treatment outcome was not based only on symptoms, but also on objective healing 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

than those of the control-diet group. Although recurrences may occur long term, good symptomatic relief and healing were provided by this method without considerable complications. The duration of calcium dobesilate treatment and the doses used were based on the authors' preliminary clinical impressions with this agent, and we cannot contradict that different regimens would be equally or more effective. In addition, "treatment failure" was decided if symptomatic and objective healing was not accomplished by the second week of the treatment. The possibility, therefore, exists that a more tolerant approach might result in a higher success rate. Nevertheless, the time of relief from symptoms in 86.21 percent of the cases averaged 5.5 days, and we do not believe it is justifiable to insist on any treatment modality that does not result in cessation of bleeding within two weeks. Patients with 1° or 2° internal hemorrhoids, who dominate in our proctology practice, were included in this study. We therefore cannot contradict that patients with more advanced stages of internal hemorrhoidal disease (3° and 4° hemorrhoids), and patients with external hemorrhoids, might also benefit from the drug, although the severe structural degeneration and distortion encountered in advanced stages might eventually require correction with surgery or outpatient mucosal fixation methods.

Especially in patients with hemorrhoids, the subepithelial layer with the vascular cushions is loosely adherent to the underlying circular muscle coat and may easily be prolapsed into the lower anal canal. The descended loose lining becomes more sensitive to pressure from straining and trauma from stool, occasionally resulting in venous distention, inflammation, erosion, bleeding, and/or thrombosis.⁵ The mucosa and submucosal vascular cushions can be fixed to the underlying muscular coat by creating submucosal fibrosis or full-thickness ulceration, by way of mucosal fixation methods, such as injection sclero-

Table 3.
The Frequencies and Percentages of the Symptom and Anitis Scores of the Control (Diet) and Study (Doxium) Groups Before and After Treatment*

	Control-diet (n = 16)	Doxium® group (n = 29)		Control-diet	Doxium® group
Symptom Score Before Treatment			Anitis Score Before Treatment		
0	—	—	0	—	—
1	—	—	1	6 (37.5%)	9 (31%)
2	16 (100%)	29 (100%)	2	10 (62.5%)	20 (69%)
Symptom Score After Treatment			Anitis Score After Treatment		
0	4 (25%)	20 (69%)	0	2 (12.5%)	15 (51.7%)
1	3 (18.8%)	6 (20.7%)	1	7 (43.8%)	12 (41.4%)
2	9 (56.3%)	3 (10.3%)	2	7 (43.8%)	2 (6.9%)

* See text for details of symptomatic and objective scoring systems.

therapy, infrared photocoagulation, or band ligation. Although the extent of fixation almost never reaches to that of surgical hemorrhoidectomy, most of these alternative fixation methods can be performed in an office setting without anesthesia, and more than 90 percent of hemorrhoidal symptoms can be successfully controlled by such nonexcisional techniques with fewer complications and pain, compared with hemorrhoidectomy.^{6, 9, 16, 17} On the other hand, mucosal fixation methods require special equipment and expertise. They are invasive techniques, and considerable side effects and complications may follow.^{7, 18, 19} Besides, we know that age-related structural changes occur in every person, while symptoms occasionally develop in only some people.^{2, 5} Therefore, especially for 1° or 2° internal hemorrhoids with minimal structural abnormality, an equally strong argument could be made for alleviating the acute attacks whenever they develop. In contrast to patients with more severe structural distortion of anal cushions (3° and 4° hemorrhoids), symptomatic treatment together with future preventive measures might be all that needs to be done.^{5, 10} In this case, we need an agent that would rapidly eliminate the acute symptoms and would be free of side effects. This study has addressed the efficacy of calcium dobesilate in treating the acute attacks; however, long-term results are lacking because of the short follow-up period. The follow-up is proceeding to document the frequency of recurrent attacks. Nevertheless, together with dietary and the above-cited preventive recommendations, a high recurrence rate is not expected in patients with early grades of hemorrhoidal disease. Besides, recurrent acute attacks are also amenable to medical treatment.

As a result of the superficial nature of hemorrhoidal disease and the general lack of life-threatening complications, most physicians prefer methods that are readily available. "Thus, a major industry, which sells ointments, cushions, heater probes, freezing devices, tablets, suppositories, foams, and food additives, has emerged."⁶ As stated before, hemorrhoidal disease is believed to be a purely clinical condition with chronic symptoms interspersed with recurrent, self-resolving acute episodes, and the possible efficacy of any intervention needs to be documented by prospective, controlled trials. A double-blind, controlled approach was, therefore, undertaken, and it deserves emphasis that more than 40 percent of the control patients improved with only diet and other preventive measures. Nevertheless, the use of calcium dobesilate provided significant advantages regarding subjective/symptomatic and objective/anoscopic healing criteria, compared with the control group. This beneficial effect was free from notable complications. Although we lack histologic data to confirm our results, the anoscopic data suggest that the beneficial effect provided by calcium dobesilate is related to the reduction in edema and anal inflammation typical of acute attacks of hemorrhoidal disease. The well-known angioprotective action of calcium dobesilate, by reducing the permeability and fragility of microvessels, restricts fluid extravasation²⁰; its reduction of plasma viscosity counteracts stasis²¹; and its antiplatelet hyperaggregability effect counteracts thrombosis.²² Calcium dobesilate possibly acts on the endothelial layer of the capillaries and reduces hyperpermeability. Its vasoprotective effects have shown some promise in the treatment of myocardial infarction.¹⁴ The reduction of high-protein edema by calcium dobesilate is

caused by both an increase in lymphatic transport and an enhanced normal proteolysis by macrophages.²³ This reduction in high-protein edema also reduces excess fibrosis and aids in normal remodeling of tissues.²⁴ In this case, calcium dobesilate was shown to be effective in certain disease states, such as chronic venous insufficiency^{11, 12} or diabetic microangiopathy.^{13, 21, 25} The combined effect of these properties of calcium dobesilate would reasonably be expected to contribute to the treatment of acute hemorrhoidal attacks, which are characterized by stasis, edema, and blood clot formation.⁵ In this study, the anoscopic inflammation scores two weeks after treatment indicated a significant reduction in macroscopic anal inflammation, regarding edema, hyperemia, and propensity to bleed. This study has confirmed, for the first time, the efficacy of calcium dobesilate in treating acute attacks of hemorrhoidal disease, based on controlled prospective data.

To avoid confounding factors caused by incomparable diets and bowel habits, the daily intake of non-starch polysaccharides (NSP) was standardized in our patient groups, and the bowel habits were monitored during the follow-up. Furthermore, encouragement was given to correct other general causes of constipation, such as ignoring the need to pass stools, irregular meals, and lack of exercise. This is our standard approach in our proctology unit, and we lack a group of patients treated only by calcium dobesilate and without dietary and lifestyle recommendations. The majority of our patients have unhealthy diet and/or bowel habits, and we find it inappropriate and unethical in a proctology unit not to teach them and only to create control groups. The diet was constituted such that it was cheap, easy to follow, and rich in NSP. NSPs are the major component of dietary fiber that reaches the colon and demonstrates the physiologic effects of fiber, namely decreased transit time, increased water retention, and the resultant formation of wet, bulky stools.^{15, 26} The amount of NSP provided with the diet used in this study is considerably high and theoretically sufficient to increase colonic movement and stool weight, although these definitive parameters were not investigated.²⁷ In accordance, 86.7 percent (39/45) of the patients developed soft bulky stools and relatively regular bowel habits soon after the initiation of the diet, whereas this was the case in 22.2 percent before the diet. According to our results, the success rate of the high-fiber diet and relative normalization of bowel habits, by itself, seems to be unsatisfactory (43.75 percent), and we still do not

believe that it is practical to insist solely on dietary measures. Nevertheless, high-fiber diet and the related bowel discipline, at the very least, do seem to possess a role in the treatment of hemorrhoidal disease, and they should be used as important adjuncts to successful treatment with any primary modality.

CONCLUSION

Calcium dobesilate treatment supplemented by high-fiber diet provided considerable symptomatic and objective improvement in patients suffering from acute attacks of 1° or 2° internal hemorrhoids. This improvement afforded by the drug caused no notable side effects, and it was significantly superior to that obtained in the control-diet group. Further data are required to comment on the long-term course of the patients with this regimen.

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