CURRENT THERAPEUTIC RESEARCH®
VOL. 62, NO. 7, JULY 2001

Calcium Dobesilate Versus Purified Flavonoid Fraction of Diosmin in the Treatment of Hemorrhoidal Crises: A Randomized, Controlled Study with an Initial Double-Blind, Double-Dummy Period

Marcos Sarabia, MD,[1] Sara León, MD,[2] Jorge Vivas, MD,[3] Maribel Lizarzabal, MD,[4] Rosa Rangel, MD,[4] José Fernández, MD,[4] Gisela Romero, MD,[4] Marianela Añez, MD,[4] María D'Albenzio, MD,[4] Zuly Latuff, MD,[4] Ana Serrano, MD,[4] and María González, MD[5]

[1]Clínica Vista Alegre, Caracas, [2]Centro Profesional, Valencia, [3]Centro Control Cáncer Gastrointestinal "Dr. Luis E. Anderson," San Cristóbal, [4]Hospital Universitario de Maracaibo, Maracaibo, and [5]Laboratorios Leti SAV, Guarenas, Venezuela

ABSTRACT

Background: Calcium dobesilate and purified, micronized flavonoid fraction of diosmin, 2 products used in the treatment of chronic venous insufficiency in the lower limbs, have been shown in open-label, placebo-controlled studies to improve symptoms of acute hemorrhoidal episodes.

Objective: This study was performed to compare the efficacy and tolerability of calcium dobesilate and purified, micronized flavonoid fraction of diosmin in the treatment of hemorrhoidal crisis.

Methods: Patients with a diagnosis of hemorrhoidal crisis were randomized to receive 1 of 2 treatments: calcium dobesilate one 500-mg capsule TID for ≥4 weeks or purified, micronized flavonoid fraction of diosmin two 500-mg capsules TID for ≥4 weeks. For the first 10 days, patients in both groups were given dummy capsules or tablets to maintain the double-blind provision. Patients underwent physical examination at baseline and after 2 days, 8 days, and 4 weeks of treatment. The following symptoms were assessed using a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe): pain, discharge, bleeding, edema, inflammation, pruritus, and anal pressure.

Results: A total of 51 patients were treated; 25 received calcium dobesilate and 26 received micronized flavonoid fraction of diosmin. In both treatment groups, significant improvement was observed in 6 of 7 evaluated symptoms after 2 days of treatment ($P < 0.05$) and in all symptoms after 4 weeks. After 4 weeks of treatment, 19 of 25 patients (76%) in the calcium dobesilate group and

Accepted for publication May 10, 2001.

0011-393X/01/$19.00

19 of 26 patients (73%) in the diosmin group were asymptomatic, with no significant differences between the 2 groups. Both products were well tolerated, and 95% to 100% of the patients were compliant with treatment.

Conclusion: Calcium dobesilate 1.5 g/d and purified, micronized flavonoid fraction of diosmin 3 g/d were equally effective and well tolerated in the treatment of signs and symptoms associated with hemorrhoidal crisis.

Key words: calcium dobesilate, hemorrhoid, purified flavonoid fraction of diosmin. (*Curr Ther Res Clin Exp.* 2001;62:524–529)

INTRODUCTION

Hemorrhoids, a pathologic dilation of the hemorrhoidal venous plexus, is a common problem worldwide. Venous insufficiency, of which hemorrhoids is 1 type, is an underestimated public health problem in industrialized countries[1] and can have a serious impact on patients' quality of life.[2]

Treatment of the acute hemorrhoidal episode involves amelioration of symptoms and long-term management through lifestyle and dietary changes aimed at restoring normal gut and bowel movements. Dietary changes to transform stool volume and consistency should be implemented. Evidence from a case-control study suggests that the habit of eating breakfast every day improves colonic reflex activity, producing a sustained decrease in the incidence of anal pathology (eg, hemorrhoids) and fistulae.[3]

The underlying cause of hemorrhoids, chronic venous insufficiency, can be treated with venotonic agents.[4] These drugs improve the structure of local capillary vessels, which are most affected by dilation and local venous insufficiency. The effects of such drugs on capillary structure (improving its permeability and resistance as well as its reactivity to endogenous amines[5,6]), their anti-inflammatory action in the local lymphatic system[7] (thereby reducing local edema), and their ability to reduce blood viscosity[8] make them useful agents in the treatment of acute hemorrhoidal episodes.

Two agents, calcium dobesilate* (calcium 2,5-dihydroxybenzenesulfonate) and a purified and micronized flavonoid fraction of diosmin† (90% diosmin and 10% flavonoids expressed as hesperidin) have been shown to improve symptoms of acute hemorrhoidal episodes.[4,9–12] These 2 drugs appear to have similar mechanisms of action, increasing tropism and capillary resistance, decreasing capillary permeability, and improving lymphatic drainage, hemorrheologic conditions, and venous contractility in response to endogenous catecholamines.[3,7]

The purpose of this randomized, prospective study was to compare the efficacy and tolerability of these 2 agents in the treatment of acute hemorrhoidal episodes.

* Trademark: Doxium® (Laboratorios Leti SAV, Guarenas, Venezuela).
† Trademark: Daflon® (Laboratorios Servier, Caracas, Venezuela).

PATIENTS AND METHODS

Patients

Male and female patients aged 18 to 75 years who came to the participating hospitals during an acute hemorrhoidal episode were eligible for enrollment. Patients had to have a diagnosis of hemorrhoidal crisis defined as symptoms of rapid onset, including pain, bleeding, discharge, edema, inflammation, or thrombosis, which when evaluated by physical examination, including rectoscopy, showed the presence of hemorrhoids and were considered responsible for the patients' symptoms. Patients with previous rectal surgery, indication for surgery, chronic or serious disease, altered hepatic or renal function, pelvic tumor, or portal hypertension were excluded.

All patients were informed about the study and gave written consent. The protocol was approved by the ethics committee of each participating institution. Patients were not allowed to take any local or systemic treatment for their hemorrhoidal condition for more than 24 hours within 5 days of study initiation.

Study Design

Patients were randomized to receive 1 of 2 treatments: calcium dobesilate 1 capsule (500 mg) TID for ≥4 weeks or purified, micronized flavonoid fraction of diosmin two 500-mg tablets TID for ≥4 weeks. For the first 10 days, patients in both groups were given dummy capsules or tablets to maintain the double-blind provision. Thus, each patient received 6 tablets and 3 capsules per day. Because of the large number of pills required to maintain the double-blind provision, and because open-label studies indicated that most patients were asymptomatic within 10 days of treatment, we discontinued the double-blind provision after 10 days. We did not include a placebo group in the study design because a previous study[4] showed that treatment with micronized flavonoid fraction of diosmin plus nonpharmacologic interventions such as Sitz baths, stool softeners, and increased fluid intake was more effective than nonpharmacologic interventions alone.

Physical examination was performed at baseline and after 2 days, 8 days, and 4 weeks of treatment. If for any reason patients could not be assessed on a Friday, the double blind was maintained until Monday. The following acute hemorrhoidal symptoms were assessed based on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe): pain, discharge, bleeding, edema, inflammation, pruritus, and anal pressure. Use of pain medication, new acute episodes, patient perception of efficacy (good, moderate, or poor), incidence of adverse events, and compliance were also assessed through direct patient interviews.

Statistical Analysis

Age, body weight, and height in the 2 groups were compared using the Student *t* test. Sex distribution, medical history, stool consistency, number of previous

crises, use of pain medication, and patient perception of efficacy were analyzed using the chi-square test. Symptoms such as pain, discharge, bleeding, edema, inflammation, pruritus, and anal pressure were analyzed using the Wilcoxon matched-pairs signed rank test for within-group differences and the Mann-Whitney *U* test for between-group differences.

The study was powered to detect a 10% within-group difference for the evaluated population, taking into account the variance for the most important parameters: pain, bleeding, and discharge.

Accepted error levels were $\alpha = 0.05$ and $\beta = 0.10$.

RESULTS

A total of 51 patients were enrolled; 25 received calcium dobesilate and 26 received purified, micronized flavonoid fraction of diosmin. At baseline, both groups were comparable with respect to sex distribution, age, body weight, height, time since last crisis, medical history, and stool consistency. There were no significant differences between groups in baseline symptom scores. Based on the physical examination and medical history, a family history of venous insufficiency, many hours in the standing or sitting position, and hard consistency of stools were common in both groups. Eighteen of 25 patients (72%) in the calcium dobesilate group and 20 of 26 (77%) in the diosmin group reported hard stools at baseline.

Significant improvement in all evaluated symptoms, with the exception of anal pressure, was observed within 48 hours of treatment in both groups, with no differences between groups at any assessment point (Table). Pain and inflammation continued to decrease significantly between 2 days and 8 days of treatment in both groups. After 4 weeks of treatment, 19 of 25 patients (76%) in the calcium dobesilate group and 19 of 26 patients (73%) in the diosmin group were asymptomatic, with no difference between treatment groups.

The differences between groups in patient perception of efficacy were not significant. In the group receiving calcium dobesilate, 76% of the patients assessed efficacy as good, 16% as moderate, and 8% as poor; in the group receiving micronized flavonoid fraction of diosmin, 73% of the patients assessed the result as good, 19% as moderate, and 8% as poor.

Analgesic intake was comparably low in both groups—4 patients (16%) in the calcium dobesilate group and 6 (23%) in the diosmin group took pain medications ($P = 0.52$).

Three patients in each group developed new hemorrhoidal crises during the treatment period.

Both products showed good tolerability. Three adverse events (cephalgia, vertigo, and colic pain) were reported in the calcium dobesilate group, and 2 (vertigo and severe anal pressure) were reported in the diosmin group.

The compliance rate in both groups was 95% to 100%.

Table. Mean hemorrhoidal symptom scores after treatment with calcium dobesilate 1.5 g/d (n = 25) or purified, micronized flavonoid fraction of diosmin 3 g/d (n = 26).

	Calcium Dobesilate				Micronized Flavonoid Fraction of Diosmin			
Symptom	Baseline	2 Days	8 Days	4 Weeks	Baseline	2 Days	8 Days	4 Weeks
Pain	1.52	0.67*	0.53*†	0.09†	1.31	0.66*	0.25*†	0.14†
Discharge	0.65	0.13*	0.04†	0.00†	0.74	0.16*	0.00†	0.00†
Bleeding	1.72	0.59*	0.28†	0.14†	1.09	0.39*	0.13†	0.05†
Edema	1.48	0.46*	0.24†	0.14†	1.43	0.66*	0.17†	0.05†
Inflammation	1.60	0.50*	0.16*†	0.05†	1.70	0.77*	0.21*†	0.05†
Pruritus	1.09	0.38*	0.28†	0.14†	0.88	0.46*	0.28†	0.18†
Anal pressure	0.88	0.43*	0.28†	0.18†	0.66	0.16	0.17	0.14†
Total	8.94	3.16*	1.81*†	0.74†	7.81	3.26*	1.21*	0.61†

Scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Baseline symptom scores did not differ significantly between treatment groups. Symptom scores at 4 weeks did not differ significantly between treatment groups.
*$P < 0.05$ versus previous period.
†$P < 0.05$ versus baseline value.

DISCUSSION

Calcium dobesilate 1.5 g/d and purified, micronized flavonoid fraction of diosmin 3 g/d were equally effective in improving hemorrhoidal symptoms within 48 hours of treatment. Substantial amelioration of all symptoms of hemorrhoidal crisis was observed in both treatment groups. The results of the present study are consistent with those from previous studies of these agents in the treatment of hemorrhoidal crisis.[10–12]

Although hemorrhoids are considered a definitive morphologic alteration, patients should be given pharmacologic therapy before treatment with more aggressive procedures like sclerosis and surgery.

A 4-week treatment period was sufficient to achieve total and sustained resolution of all hemorrhoidal symptoms assessed; patients treated for 12 weeks did not show additional benefits. Both treatments were well tolerated, and compliance with treatment was >90% in the 2 groups.

CONCLUSION

Treatment with calcium dobesilate 1.5 g/d was as effective as treatment with purified, micronized flavonoid fraction of diosmin 3 g/d in improving hemorrhoidal symptoms within 48 hours of treatment. Both treatments were equally well tolerated.

ACKNOWLEDGMENT

The authors thank Ms. Carmen Zulay Ibarra for her collaboration in performing the statistical analysis.

REFERENCES

1. Van den Oever R, Hepp B, Debbaut B, Simon I. Socio-economic impact of chronic venous insufficiency. An underestimated public health problem. *Int Angiol.* 1998;17: 161–167.
2. Sailer M, Bussen D, Debris ES, et al. Quality of life in patients with benign anorectal disorders. *Br J Surg.* 1998;85:1716–1719.
3. Ahmed SK, Thompson HJ. The effect of breakfast on minor anal complaints: A matched case-control study. *J R Coll Surg Edinburgh.* 1997;42:331–333.
4. Cospite M. Double-blind, placebo-controlled evaluation of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids. *Angiology.* 1994;45:566–573.
5. Galley P. Etude de l'activité de Daflon 500 mg sur la résistance capillaire. *J Int Med.* 1987;88(Suppl):25–26.
6. Hasslacher C, Kopischke HG, Burklin E. Inhibition of increased capillary basement membrane synthesis in diabetic rats [in German]. *Vasa.* 1981;10:148–150.
7. Piller NB. The lymphagogue action of calcium dobesilate on the flow of lymph from the thoracic duct of anesthetized and mobile guinea pigs. *Lymphology.* 1988;21:124–127.
8. Barras JP, Graf C. Hyperviscosity in diabetic retinopathy treated with Doxium (calcium dobesilate). *Vasa.* 1980;9:161–164.
9. Cospite M, Cospite V. Treatment of hemorrhoids with Daflon® 500 mg. *Phlebology.* 1992;7(Suppl 2):53–56.
10. Bermúdez L. Dobesilato de calcio (Doxium®) en el tratamiento de las crisis hemorroidales. *Arch Ven Farm Ther.* 2000;19:49–52.
11. Godeberg P. Daflon® 500 mg is significantly more effective than placebo in the treatment of hemorrhoids. *Phlebology.* 1992;7(Suppl 2):57–59.
12. Launois R. At the crossroads of venous insufficiency and hemorrhoidal disease: Daflon 500 mg—repercussions of venous insufficiency on everyday life. *Angiology.* 1994;45:495–504.

Address correspondence to:
María González, MD
Laboratorios Leti SAV, Edif. Laboratorios Leti, Dirección Médica
Zona Industrial del Este, Avenida 2
Guarenas, Miranda 1220
Venezuela