Clinical Trial of Oral Diosmin (Daflon®) in the Treatment of Hemorrhoids

Wuttichai Thanapongsathorn, M.D.,
Tanit Vajrabukka, B.Sc., M.B., C.H.B., F.R.C.S. (Ed)

From the Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

A double-blind, comparative, controlled study on the effectiveness of the addition of oral diosmin (Daflon®; Lab. Servier, Orléans, France) and placebo to a conservative regime of bulk laxative in the treatment of acute symptoms of first-degree and second-degree internal hemorrhoids was undertaken in 100 patients. The diosmin and placebo groups, with 50 patients each, were comparable in age, sex, symptoms, and the severity of the underlying hemorrhoids. During the first four days, the patients received 12 tablets in three divided doses, and then they received two tablets twice daily for another 10 days. Subjective and objective changes were assessed at the 4th and 14th days of treatment. The diosmin group showed statistically significant objective improvement ($P < 0.01$) without accompanying subjective improvement on the fourth day. However, at day 14, there was no significant difference in either subjective or objective improvement between the two groups. Two cases in the placebo group were taken out of the trial on the fourth day owing to clinical deterioration. No side effect of diosmin was detected in this study. [Key words: Hemorrhoids; Oral antihemorrhoid drugs; Diosmin]

Thanapongsathorn W, Vajrabukka T. Clinical trial of oral diosmin (Daflon®) in the treatment of hemorrhoids. Dis Colon Rectum 1992;35:1085–1088.

There are many oral antihemorrhoid preparations widely prescribed by Thai physicians in the treatment of acute symptoms of hemorrhoids. These preparations contain semisynthetic agents or plant extracts such as escin, diosmin, and rutin-related compounds that have been shown to have regulatory effects on veins, venules, and capillaries.[1-3] Although there are many reports of their efficacy in the treatment of hemorrhoids from various medical centers in continental Europe, only a very few double-blind trials exist and their results are conflicting.[4-6] In this report, a commercial preparation, Daflon®, each tablet containing flavonoid extracts of Rutaceae corresponding to 150 mg of diosmin, was used in a double-blind, comparative, controlled study in an attempt to evaluate its efficacy in the treatment of acute symptoms of first-degree and second-degree hemorrhoids.

Daflon® is the first therapeutic application of diosmin. It was launched commercially in France in 1971 by les Laboratoires Servier for the treatment of venous insufficiency of the lower limb and of acute symptoms of hemorrhoids. The drug is now marketed in 57 countries worldwide, including eight countries in western Europe. Its application has been extended to include many other venocapillary disorders such as varicose veins, venous stasis ulcer, subconjunctival and retinal hemorrhage, and gingival bleeding. Daflon® has been shown to act on the entire venocapillary and lymphatic systems of the return microcirculation,[1-3] thereby increasing venous tone, enhancing capillary resistance, restoring normal capillary permeability, accelerating lymphatic drainage, as well as reducing inflammatory reaction. It is nontoxic and may be given orally without loss of efficiency. In the treatment of acute symptoms of hemorrhoids, the manufacturer recommends 12 tablets daily in three divided doses for four days to obtain rapid relief and then four tablets daily in two divided doses for another 10 to 30 days.

MATERIALS AND METHODS

The number of patients necessary for such comparative evaluation was calculated to be at least 100 using a sample size technique ($Z_A = 0.05$ and $Z_B = 0.10$; two-way test). Accordingly, 100 new and consecutive patients with acute symptoms due to first-degree and second-degree internal hemorrhoids by the criteria of Goligher[7] were entered into the trial during July 1987 to August 1987 at the colorectal clinic of Chulalongkorn Hospital. Each patient had a history and general physical examination, including an anoscopic examination, completed and recorded at the beginning day (D_0), the fourth day (D_4), and the 14th day (D_{14}), using

Address reprint requests to Dr. Thanapongsathorn: Department of Surgery, Chulalongkorn Hospital, Bangkok 10330, Thailand.

diagrams demonstrating number, size, site, and bleeding points of hemorrhoids. Care was taken to exclude the following conditions from this study: surgical anorectal diseases (thrombosed external hemorrhoids, strangulated internal hemorrhoids, anal fissures, fistula-in-ano, and anorectal abscesses), previous internal hemorrhoid treatment, pregnancy, portal hypertension, and hematologic diseases. Barium enema and sigmoidoscopy were done when indicated. The patients were randomly allocated without the assessing surgeon's knowledge into two equal groups of 50, with one group receiving placebo (starch) and another receiving oral diosmin. All patients took 12 tablets of either placebo or diosmin in three divided doses during the first four days and then two tablets twice daily for another 10 days, the dose schedule being the manufacturer's recommended dosage. The patients were prescribed a bulk laxative (psyllium seed; Metamucil®; Procter & Gamble, Cincinnati, OH), 11 g of which were taken once daily at bedtime during the period of study. They were encouraged to take a high-fiber diet and plenty of water and to avoid alcohol and spicy food. A warm sitz bath at least once a day was recommended. Effectiveness of treatment was assessed in relation to subjective symptoms of bleeding (s1), pain (s2), prolapse (s3), burning (s4), pruritus (s5), tenesmus (s6), and heaviness (s7) and also in relation to the objective signs of swelling (o1), congestion (o2), bleeding (o3), exudation (o4), and prolapse (o5).

The severity of the symptoms and signs was graded by the same observer using a score from 0 to 3 as follows: 0 = no symptoms or signs; 1 = mild; 2 = moderate; and 3 = severe. The total scores on D_0, D_4, and D_{14} in each patient were compared. A score less than that on D_0 indicated improvement, and a score equal to or more than that on D_0 indicated no change or deterioration, respectively. Only patients with improvement were selected for statistical evaluation using the chi-squared test. The patients who became worse were taken out of the study and had further treatment.

Adverse effects of diosmin were assessed by questionnaire and general physical examination.

RESULTS

The relevant clinical features of patients in both groups were compared as shown in Table 1.

On the fourth day of treatment, subjective and objective improvements among the placebo group were 60 percent and 22 percent, while similar improvements in the diosmin group were 74 percent and 52 percent, respectively. Two patients in the placebo group had to be taken out of the study owing to subjective and objective deterioration. By chi-squared test, the improvement in objective signs on D_4 in the diosmin group had statistical significance ($P < 0.01$), especially in relation to swelling (o1) and congestion (o2) (Table 2 and Fig. 1).

On D_{14}, subjective and objective improvements, among the placebo group were 94 percent and 67 percent, while improvements in the diosmin group were 98 percent and 72 percent, respectively (Table 3 and Fig. 2). The chi-squared test showed no statistically significant difference as a whole between the two groups.

Details of responses according to severity of hemorrhoids were as shown in Tables 4 and 5. No adverse effects of placebo or diosmin were detected during the treatment.

Table 1.
Clinical Features of Patients in Both Groups

	Placebo	Diosmin
Sex (male/female)	19/31	22/28
Average age (yr)	32	32
Family history of hemorrhoids	17 (34%)	23 (46%)
History of alcohol consumption	15 (30%)	12 (24%)
Constipation*	40 (80%)	41 (82%)
History of laxative usage	14 (28%)	17 (34%)
Degree of hemorrhoids (first/second)	15/35	18/32
Average duration of symptoms (days)	7	9

* Hard and dry stools associated with strain on defecation.

Table 2.
Results of Treatment on D_4

	Subjective		Objective	
	Placebo	Diosmin	Placebo	Diosmin
Improved	30 (60%)	37 (74%)	11 (22%)	26 (52%)
Unchanged	18 (36%)	13 (26%)	37 (74%)	24 (48%)
Worse	2* (4%)	0 (0%)	2* (4%)	0 (0%)
Totals	50	50	50	50
	$\chi^2 = 2.21$ P = NS		$\chi^2 = 9.65$ $P = 0.01$	

* Two cases were taken out of the trial.
NS = no significance.

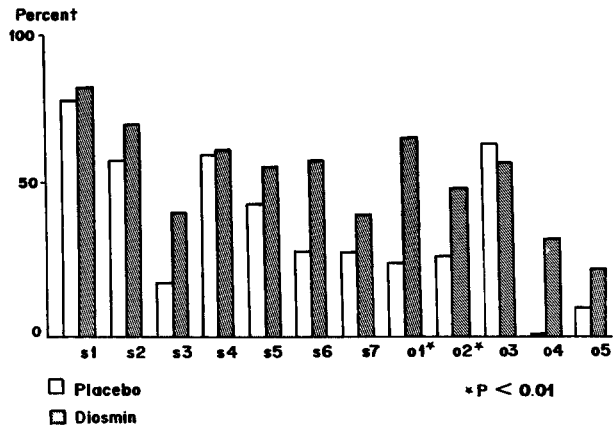

Figure 1. Subjective and objective improvement on D_4. s1, bleeding; s2, pain; s3, prolapse; s4, burning; s5, pruritus; s6, tenesmus; s7, heaviness; o1, swelling; o2, congestion; o3, bleeding; o4, exudation; o5, prolapse.

Table 3.
Results of Treatment on D_{14}

Improved	Subjective		Objective	
	Placebo	Diosmin	Placebo	Diosmin
Improved	45 (94%)	49 (98%)	32 (67%)	36 (72%)
Unchanged	3 (6%)	1 (2%)	14 (24%)	14 (28%)
Worse	0 (0%)	0 (0%)	2 (4%)	0 (0%)
Totals	48	50	48	50
	$\chi^2 = 0.31$ P = NS		$\chi^2 = 0.74$ P = NS	

NS = no significance.

Table 4.
Results of Treatment on D_4 According to Severity of Hemorrhoids

	Subjective		Objective	
	Placebo (1°/2°)	Diosmin (1°/2°)	Placebo (1°/2°)	Diosmin (1°/2°)
Improved	11/19	12/25	2/9	11/15
Unchanged	4/14	6/7	13/24	7/27
Worse	0/2*	0/0	0/2*	0/0
Totals	15/35	18/32	15/35	18/32

* Two cases were taken out of the trial.
1° = first-degree hemorrhoids.
2° = second-degree hemorrhoids.

DISCUSSION

Although there are many views on the nature of hemorrhoids,[8] most consider constipation and undue straining to be important contributing factors in the genesis of acute symptoms. It is natural that simple and appropriate measures to prevent constipation and straining, such as high-fiber diet or bulk laxative, together with dietary discretion and better local hygiene, should form the minimal or basic care of patients with acute symptoms while awaiting more definite treatment. The effectiveness of such a regime has been reported[9, 10] and confirmed by the achievement of the placebo group in this study. It is debatable whether bulk laxative should be included in this study, but it seems unethical not to provide at least a minimal and effective treatment for the patients in the placebo group.

Table 5.
Results of Treatment on D_{14} According to Severity of Hemorrhoids

	Subjective		Objective	
	Placebo (1°/2°)	Diosmin (1°/2°)	Placebo (1°/2°)	Diosmin (1°/2°)
Improved	15/30	18/31	12/20	16/20
Unchanged	0/3	0/1	3/11	2/12
Worse	0/0	18/32	15/33	18/32
Totals	15/33	18/32	15/33	18/32

1° = first-degree hemorrhoids.
2° = second-degree hemorrhoids.

Although diosmin in this study significantly reduced swelling and congestion of hemorrhoids at D_4 compared with placebo, such a beneficial effect was not seen on D_{14}, and the objective improvement was not enough to be felt by the patients when the changes in the symptoms were assessed as a whole. This must be at least in part due to the effectiveness of the basic regime in the relief of symptoms such that it is difficult to discern an

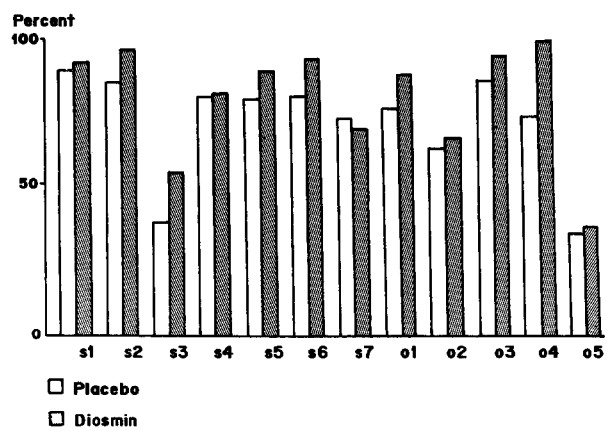

Figure 2. Subjective and objective improvement on D_{14}. s1, bleeding; s2, pain; s3, prolapse; s4, burning; s5, pruritus; s6, tenesmus; s7, heaviness; o1, swelling; o2, congestion; o3, bleeding; o4, exudation; o5, prolapse.

additional benefit of the added diosmin. It may also be due to inadequate sampling size to demonstrate the efficacy of diosmin in this disorder, which often regresses spontaneously as evident in the placebo group of many studies.[9, 10] In this context it can be seen that analysis according to the severity of hemorrhoids (Tables 4 and 5) showed an advantage of diosmin over placebo at D_4 in both subjective and objective responses in patients with second-degree hemorrhoids and in the objective response in patients with first-degree hemorrhoids, but the patients in each category were too few for statistical evaluation. It can only be speculated here that, with a larger patient population, these advantages of diosmin over placebo might achieve statistical significance.

It must be concluded that this trial showed the benefit of adding diosmin to the conservative regime of bulk laxative to be slight, short-lived, and not noticeable by the patients.

SUMMARY

The effects of adding oral diosmin and placebo to a basic conservative regime of bulk laxative in the treatment of acute symptoms of hemorrhoids were evaluated in a prospective, double-blind, comparative, controlled study in 100 patients with first-degree and second-degree hemorrhoids. Four days of treatment with diosmin resulted in significant improvement in swelling and congestion of the hemorrhoids without corresponding symptomatic improvement. After 14 days of treatment, no significant difference could be detected in the improvement of symptoms or signs in both groups. No side effect of diosmin was detected in this study.

REFERENCES

1. Desnoyers P. General pharmacological review of Daflon. In: European symposium on venous disease and its treatment. Rome, April 1978. Selected papers published by Gazette Medicale de France, 1987: 17–21.
2. Kissel P, Royer R. Contribution au traitement de la maladie veineuse, Etude par la plethysmographie gazeuse d'un nouveau prineipe vaso-actif. Therapeutique 1970;46:907–9.
3. Klemn J. Clinical and pharmacological study of the venous action of Daflon using the clearance of xenon 133. Gazette Medicale de France 1976;83:3158–65.
4. Annoni F, Boccasanta P, Chiurazzi D, Mozzi E, Oberhauser V. Treatment of acute symptoms of hemorrhoid disease with high-dose oral 0-(beta-hydroxyethyl) rutosides. Minerva Med 1986;77:1663–8.
5. Thorp RH, Hughes ES. A clinical trial of trihydroxyethyl-rutoside ("VAREMOID") in the treatment of hemorrhoid. Med J Aust 1970;2:1076–8.
6. Clyne MB, Freeling P, Ginsborg S. Troxerutin in the treatment of hemorrhoids. Practitioner 1967;198: 420–3.
7. Goligher JC. Surgery of the anus, rectum and colon. 5th ed. London: Bailliere Tindall, 1984:101.
8. Thomson WS. The nature of haemorrhoids. Br J Surg 1975;62:542–52.
9. Webster DJ, Gough DC, Craven JL. The use of bulk evacuant in patients with haemorrhoids. Br J Surg 1978;65:291–2.
10. Moesgaard F, Nielsen ML, Hansen JB, Knudsen JT. High-fiber diet reduces bleeding and pain in patients with hemorrhoids. Dis Colon Rectum 1982;25: 454–6.