Chulalongkorn Medical Journal

Volume 38
Issue 2 *February 1994*

Article 3

2-1-1994

Therapeutic activity of Daflon 500 mg(R) in acute episodesof hemorrhoids

Tanit Vajrabukka

Arun Rojanasakul

Vithya Vathanophas

Narong Lertakyamanee

Paitoon Juangbhanit

See next page for additional authors

Therapeutic activity of Daflon 500 mg(R) in acute episodesof hemorrhoids

Authors

Tanit Vajrabukka, Arun Rojanasakul, Vithya Vathanophas, Narong Lertakyamanee, Paitoon Juangbhanit, Supong Khamkosit, Bunlue Chaleoykitti, Tundom Chirabandhu, Kasem Kiatpanabhikul, Sukij Panpimanmas, Apinop Chanvitan, Chusak Kuptanond, Paisit Siriwittayakom, and Paisit Siriwittayakom

นิพนธ์ต้นฉบับ

Therapeutic activity of Daflon 500 mg(R) in acute episodes of hemorrhoids.

Tanit Vajrabukka*
Vithya Vathanophas**
Paitoon Juangbhanit***a
Bunlue Chaleoykitti****
Kasem Kiatpanabhikul*****
Apinop Chanvitan******
Paisit Siriwittayakorn********
Arun Rojanasakul*
Narong Lertakyamanee**
Supong Khamkosit***b
Tundorn Chirabandhu****
Sukij Panpimanmas*****
Chusak Kuptanond*******
Sunthorn Thaisamakr*********

Vajrabukka T, Rojanasakul A, Vathanophas V, Lertakyamanee N, Juangbhanit P, Khamkosit† S, Chaleoykitti B, Chirabandhu T, Kiatpanabhikul K, Panpimanmas S, Chanvitan A, Kuptanond C, Siriwittayakorn P, Thaisamakr S. Therapeutic activity of Daflon 500 mg(R) in acute episodes of hemorrhoids. Chula Med J 1994 Feb; 38(2) :77-83

In this double blind, randomized, placebo controlled trial conducted in 9 Thai centers, the efficacy of the 7 day course of treatment with Daflon 500 mg(R) in acute episodes of hemorrhoids was demonstrated on the basis of overall assessment of improvement of the whole attack. Evaluation of individual symptoms showed significant difference in favor of Daflon 500 mg(R) in the evolution of discharge. For the remaining symptoms, in spite of a trend in favor of Daflon 500 mg(R) the statistical analyses performed could not domonstrate significant difference between Daflon 500 mg(R) and placebo. This discrepancy between global and separate assessment of symptomatology and the lack of statistical significance in the latter probably resulted from an unusually high percentage of placebo responders in this trial and a rapid spontaneous disappearance of symptoms which could not have been taken into account by a relative delay in the treatment (up to 3 days of disease duration) and check of efficacy (2nd day of treatment). Signs were not clearly improved.

Key words : *Hemorrhoids. Dation 500 mg, Diosamine*

Reprint request : Vajrabukka T, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. October 1, 1993.

* Department of Surgery, Faculty of Medicine, Chulalongkorn University.
** Department of Sugery, Siriraj Hospital.
***a Department of Medicine, Bhumiboladulyadej Hospital.
***b Department of Surgery, Bhumiboladulyadej Hospital.
**** Department of Sugery, Pramongkutklao Hospital.
***** Department of Surgery, Rajvithee Hospital.
****** Department of Surgery, Songklanakarin Hospital.
****** Department of Surgery, Srinakarin Hospital, Khon Kaen.
******** Department of Surgery, Maharaj Hospital, Chiengmai.
********* Department of Medicine, Maharaj Hospital, Nakorn Rajsrima.

ธนิต วัชรพุกก์, อรุณ โรจนสกุล, วิทยา วัฒโนภาส, ณรงค์ เลิศอรรฆยมณี, ไพฑูรย์ จ๋วงพานิช, สุพงษ์ เขมโฆษิต, ฉัตรชัย ทัศนียานนท์, บรรลือ เฉลยกิตติ, ธัญดร จีระพันธ์, เกษม เกียรติปานอภิกุล, สุกิจ พันธุ์พิมานมาศ, อภินพ จันทรวิทัน, ชูศักดิ์ คุปตานนท์, ไพศิษฐ์ ศิรวิทยากร, สุนทร ไทยสมัคร. ผลการใช้ยา เดฟลอน 500 มก. (R) ในการรักษาอาการของโรคริดสีดวงทวาร. จุฬาลงกรณ์เวชสาร 2537 กุมภาพันธ์; 38(2) : 77-83

รายงานผลการทดลองแบบ prospective, randomized, double-blind ในโรงพยาบาล 9 แห่ง จำนวนผู้ป่วยทั้งหมด 226 คน โดยใช้ยา Daflon 500 mg.(R) เปรียบเทียบกับ placebo รักษาโรคริดสีดวงทวารภายใน ซึ่งมีอาการมาก่อนการทดลองไม่เกิน 3 วัน ระยะเวลาที่ใช้รักษา 7 วัน

เมื่อประเมินความเปลี่ยนแปลงของอาการแต่ละอย่างแยกกัน พบว่า ยา Daflon 500 mg(R) ทำให้อาการกันแฉะ (discharge) ดีขึ้นกว่าการใช้ placebo อย่างชัดเจน แต่ไม่พบผลต่างที่เด่นชัดระหว่าง ยา Daflon 500 mg(R) กับ placebo ในการรักษาอาการอื่น ๆ ได้แก่ เลือดออก (bleeding), ปวดกัน (pain) และไม่สบายกัน (anal discomfort) การเปลี่ยนแปลงรูปลักษณะของหัวริดสีดวงทวารภายใน ไม่แตกต่างกันในผู้ป่วยทั้งสองกลุ่ม เมื่อประเมินการเปลี่ยนแปลงการดำเนินโรคโดยพิจารณาอาการ ทั้งหมดร่วมกันพบว่าในผู้ป่วยพอใจการรักษาด้วยยา Daflon 500 mg(R) โดยมีผลตอบสนองในระดับดี มากและดีชัดกว่ากลุ่ม placebo และจำนวนผู้ที่อาการหายขาดในกลุ่มที่ได้รับยา Daflon 500 mg(R) มีมากกว่ากลุ่ม placebo

Diosmine and hesperidine are flavonoids extracted from plant (Citrus limon Linn., Rutaceae). Both compounds are nontoxic and known to be pharmacologically active, especially diosmine, in increasing venous tone, improving capillary resistance, restoring capillary permeability as well as reducing edema and acute inflammation.(1-3) Because of their properties, and oral preparation, Daflon(R) (Les Laboratoires Servier, France) containing diosmine 150 mg. was introduced for the treatment of hemorrhoids in 1971 in France and Western Europe and in 1983 in Thailand with varying results.(4-6)

Daflon 500 mg(R) is new oral preparation containing 450 mg diosmine and 50 mg hesperidine in micronized form for better absorption. In this report, the efficacy of Daflon 500 mg(R) in the treatment of acute episodes of hemorrhoids is assesed by a prospective double blind, placebo controlled trial in 9 centers in Thailand.

Method

The patients over 18 years of age and non pregnant attending outpatient departments at collaborative centers with acute symptoms of hemorrhoids no longer than 3 days were included in the study. The symptoms occuring in various combination were pain, discomfort, bleeding and discharge. All patients received general physical examination as well as proctoscopic examination to ensure that the symptoms were related to hemorrhoids. Excluded from the trial were those with permanently prolapsed hemorrhoids (grade 4) or those with associated anorectal diseases such as anal fissure, fistula-in-ano and abscesses. The patients received identical boxes of tablets which were either the drug or placebo (starch) according to the random number unknown to the prescribing physicians. Three tablets were taken twice daily for 4 days and then 2 tablets twice daily for another 3 days, altogether 36 tablets in 7 days. The patients received usual instruction regarding proper anal hygiene and were encouraged to take high fiber diet and plenty of water. They were instructed not to take any additional medication during the 7 days of treatment. At the end of treatment (day 7 or D7) the patients were seen together with the medication boxes and the remaining tablets, if any, were counted.

Information recording

At inclusion (day 0 or D0) each patient received a self-rating chart into which he entered the degrees of severity of symptoms daily from D0 to D7 according to the scale : severe = 3, moderate = 2, mild = 1, none = 0. This chart was to be presented to the investigator at D7 so that the investigator could judge the daily improvement that might have occurred. The patients had to state at the end of the trial (D7) whether they were very satisfied, satisfied or not satisfied with the efficacy of the treatment.

The investigator recorded the severity of symptoms and signs of each patient on the day of inclusion (D0) and at the end of the trial (D7) using similar numerical scale. The investigator also recorded his impression at the end of the trial (D7) for each patient whether the therapy appeared very good, good, useful or useless. He examined the patients' self-rating charts at D7 and recorded the degree of overall improvement daily from D2 to D7 using numerical scale : 0 = nil, 1 = notable improvement, 2 = significant improvement, 3 = disapperance or cure.

Evaluation of efficacy

As a whole evaluation was made in the change over time from D0 to D7 of individual symptoms as well as overall changes assessed from both patients' as well as from investigators' data. Statistical methods were Cochran-Mantel-Haenszel Chi-square test or Wilcoxon test (survival curve).

Results

Of the 259 patients who entered the trial only 226 patients could be accepted for analysis of efficacy as 16 did not finish the trial and 17 showed major deviation from the protocol. Of the 226 patients 121 were in Daflon 500 mg(R) group and 105 in placebo group. Both groups were compatible in demographic data (Table 1), previous history of hemorrhoids (Table 2), symptoms (Table 3) and signs (Table 4) of hemorrhoids on presentation. Analysis of habit showed no statistical differences in the 2 groups regarding alcohol consumption (p=0.143), intake of spicy foods (p=0.131) and tobacco (p=0.603). The results of efficacy analysis were shown in Figures 1,2 and Tables 5,6,7.

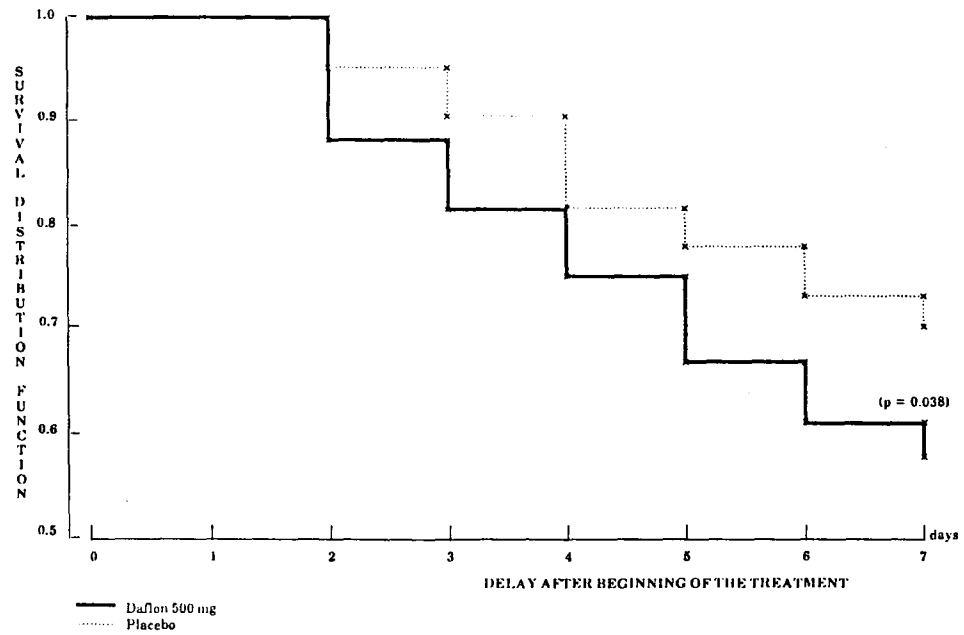

Figure 1. Time of Disappearance of Acute Episodes (Survival curve).

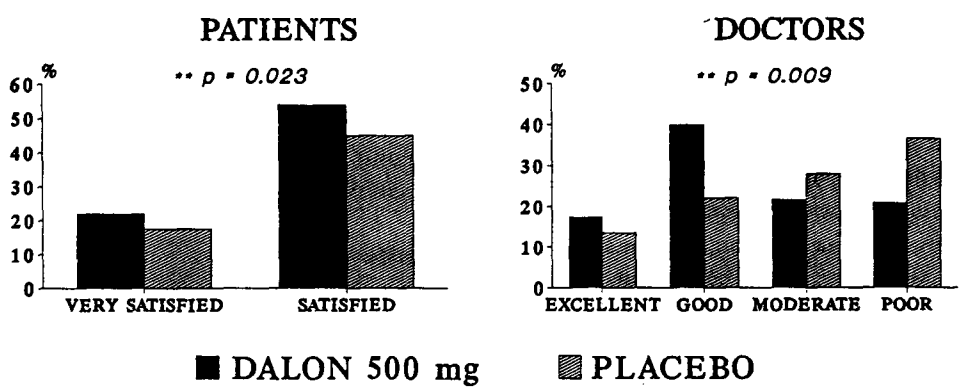

Figure 2. Overall Assessment of Activity.

Table 1. The demographic data of the 2 groups.

	Daflon 500 mg. (n=121)	**Placebo (n=105)**	**P**
Sex (males)	47.90%	52.40%	0.505
Age (years)	35.1+ 12.1	37.0+12.3	0.233
Body mass index (kg/m2)	21.3+ 3.3	21.8+ 3.1	0.217

Results are expressed as mean + S.D.

Table 2. Previous history of hemorrhoidal disease.

Criteria	Daflon 500 mg. (n=121)	Placebo (n=105)	P
Time elapsed since the first attack (months)	46.7+ 56.	46.8+ 63.5	0.989
Number of attacks in the year preceding inclusion	3.8+ 5.5	4.2+ 7.2	0.639
Mean duration of previous attacks (days)	5.1+ 4.4	5.6+ 5.1	0.448
Mean intensity of previous attacks (%)			
- mild	21.1	12.2	
- moderate	53.2	69.4	0.053
- severe	25.7	18.4	
Stage of internal hemorrhoids (%)			
- first degree	28.1	20	
- second degree	58.7	69.5	0.234
- third degree	13.2	10.5	
Duration of attack at inclusion (%)			
- 3 days or less	87.5	81.3	
- between 3 and 5 days	7.4	15.5	0.354
- longer than 5 days	5.1	3.2	

Results are expressed as mean +S.D.

Table 3. The number and percentage of patients in 2 groups presenting with each symptom at D0.

	Daflon 500 mg. (n=121) n%	Placebo (n=105) n%	P
Anal discomfort	85(70.8%)	73(69.5%)	0.341
Pain	88(73.3%)	78(74.2%)	0.292
Rectal bleeding	95(79.2%)	93(88.6%)	0.241
Discharge	54(45.0%)	46(43.8%)	0.742

Table 4. The number and percentage of patients in 2 groups showing individual signs at D0.

	Daflon 500 mg. (n=121) n%	Placebo (n=105) n%	P
Thrombosed external	10(8.4%)	14(13.5%)	0.383
Thrombosed internal	73(60.8%)	63(60.0%)	0.692
Proctitis (congestion)	55(45.8%)	40(38.5%)	0.692
Reducible prolapse	54(45.0%)	50(47.6%)	0.783

Table 5. Patients' self assessment on efficacy showing the significant levels of differences between the Daflon 500 mg. and placebo treated groups.

Symptoms	Complete disappearance of Symptoms (Survival Curve-Wilcoxon test)	Improvement of Symptoms (C.M.H. test)	
		D0/D2	D0/D7
Discharge	NS +	0.038	NS + +
Anal discomfort	NS +	NS + +	NS + +
Pain	NS +	NS	NS
Rectal bleeding	NS +	NS + +	NS +

C.M.H. test : Cochran Mantel-Haenszel test
NS : not significant
NS + : not significant but effect of Daflon 500 mg. > effect of placebo
NS + + : not significant but close to significant threshold ($p<0.1$)

Table 6. Investigators' assessment of efficacy showing the significant levels of difference between the Daflon 500 mg. and placebo treated groups.

	Complete disappearance of Symptoms (Survival Curve-wilcoxon test)	Improvement of Symptoms (C.M.H. test)	
		D0/D2	D0/D7
Whole attack	0.038	0.005	0.047
Symptoms	Intensity of Symptoms (C.M.H test) D0/D7	Improvement of Symptoms (C.M.H. test) D0/D7	
Discharge	0.001	NS +	
Anal discomfort	NS +	NS +	
Pain	NS +	NS +	
Rectal bleeding	NS +	NS +	

C.M.H. test : Cochran Mantel-Haenszel test
NS + : not significant but effect of Daflon 500 mg.> effect of placebo
NS ++ : not significant but close to the significant threshold ($p<0.1$)

Table 7. Number and percentage of patients showing improvement of individual symptoms at D7. Data from patients own assessment as an example of high placebo response.

	Daflon 500 mg.	Placebo	P
Anal discomfort	57/28 (67.1%)	39/30 (56.8%)	0.185
Pain	69/15 (82.1%)	66/12 (84.6%)	0.673
Rectal bleeding	79/13 (85.9%)	73/17 (81.1%)	0.378
Discharge	40/11 (78.9%)	27/15 (64.7%)	0.111

The results are expressed as ratio of patients showing improvement/ non-improvement of individual symptoms at D7. % improvement of individual symptoms in each group is shown in the bracket.

Discussion

The efficacy of the 7 day course of Daflon 500 mg(R) on acute episodes of hemorrhoids in this double blind prospective trial appears in many types of overall assessment from both patients and investigators' data. At the end the patients were more satisfied when treated with Daflon 500 mg(R) than with placebo (Figure 2). The investigators noted in the Daflon 500 mg(R) group significantly more excellent and good results (Figure 2). The investigators found higher proportion of sustaining improvement among patients treated with Daflon 500 mg(R) starting from the second day of treatment through to the end of the trial (Table 6). The superiority of Daflon 500 mg(R) was also demonstrated by the statistical analysis of the survival curve featuring complete disappearance of all symptoms (Figure 1).

The situation is less clear when the evolution of individual symptoms and signs were considered separately. For discharge, significant improvement was found in the Daflon 500 mg(R) group at D2 by the patients (Table 5) and a significant decrease in the intensity of the symptom at D7 was noted by the investigators (Table 6). For the remaining symptoms analysis only showed a trend in favor of Daflon 500 mg(R) over placebo in most tests without reaching statistically significant level. There were no differences in the evalution of signs between the two groups. The discrepancy between global and separate assessment of symptomatology and the lack of statistical significance in the latter despite a trend in favor of the Daflon 500 mg. group must by and large have arisen from the difficulty in statistical analysis posed by the unexpectedly high placebo response (Table 7). The high placebo response made it very difficult to see the efficacy of the drug clearly particularly in the improvement of individual symptoms although the efficacy was seen with the overall assessments which probably represented the summation of small improvement of each individual symptoms.

The high placebo response can be attributed to several factors. The majority of patients in this study already had symptoms of hemorrhoids for almost 3 days at inclusion while the average duration of previous attacks lasted only 5 days (Table 2). Hence it is probable that most patients were already on the verge of spontaneous recovery at inclusion. Some patients might have taken other anti-hemorrhoidal drugs during the trial contrary to their doctors' warning as anti-hemorrhoidal preparations are easily obtainable without prescription. It is also a well-known fact that most Thai patients are eager to please their doctors and so they might have biased their response accordingly.

In retrospect the differences between Daflon 500 mg(R) and placebo would be more clearly shown if the trial were modified to overcome the problems posed by high placebo response and rapid spontaneous resolution of symptoms. However, some of the modifications could be difficult to accomplish in the actual clinical trial setting. For examples, more patients with earlier symptom should be recruited to compensate for the rapid spontaneous resolution of symptoms. By the same token, earlier assessment of responses to the treatment should be done. Patients with thrombosis should be excluded as satisfactory response usually takes longer than 7 days with any kind of conservative treatment. The study should concentrate on earlier stages (I and II) of hemorrhoids as their responses would be affected less by the time constraint of the study than those with larger hemorrhoids. Finally, the analyses would be more meaningful with fewer symptoms and signs which are clear-cut such as bleeding or discharge or congestion while avoiding overlapping stratification such as discomfort and pain.

Acknowledgements

The investigators wish to acknowledge with thanks the assistance rendered in the trial by Les Laboratoires Servier, Thailand and France.

References

1. Desnoyers P. General pharmacological review of Daflon (English translation). In : European Symposium on Venous Disease and its Treatment. Rome, April 1978 : 74-8
2. Kissel P, Royer R. Contribution au traitement de la maladie veineuse. Etude par la plethy smographie gazeuse d'un nouveau principe vasoactif (English translation). Therapeutique 1970 Nov; 46 : 907-9
3. Klemm J. Clinical and pharmacological study of the venous action of Daflon using the clearance of xenon 133 (English traslation). Gaz Med France 1976; 83(31) : 3158-65
4. Ljunggren B, Martin JP. The treatment of haemorrhoids by Daflon at a dosage of 12 tablets per day (English translation). Gaz Med France 1975; 82(12) : 1412-4
5. Panijayanond P, Chotiprasidhi P. The role of Daflon (R) the treatment of acute hemorrhoids. J Med Assoc Thai 1985 Feb; 68(2) : 72-80
6. Thanapongsathorn W, Vajrabukka T. A clinical trial of oral diosmine (Daflon(R)) in the treatment of hemorrhoids. Dis colon Rectum 1992 Nov; 35(11) : 1085-8 OPT