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ORIGINAL ARTICLE

Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of I–III degree hemorroidal disease: a double-blind multicenter prospective comparative study

Italo Corsale[1] · Paolo Carrieri[2] · Jacopo Martellucci[3] · Alessandro Piccolomini[4] · Luigi Verre[4] · Marco Rigutini[1] · Sonia Panicucci[1]

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Abstract

Purpose We evaluated the efficacy of new flavonoids mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) to reduce bleeding from I–III degrees hemorrhoidal disease in the short and medium time.

Methods One hundred fifty-four consecutive patients with hemorrhoidal disease recruited in four colorectal units were enrolled to the study. Exclusion criteria were allergy to the flavonoids, inflammatory bowel disease, obstructed defecation syndrome, pregnancy and puerperium, associated anal disease or hemorrhoidal thrombosis, proctologic surgical procedures within 1 year before recruitment, contemporary cancer or HIV, previous pelvic radiotherapy, patients receiving oral anticoagulant therapy, or contemporary administration of other therapy for hemorrhoids. Patients with inability to understand the study or mental disorders were also excluded.

Results Seventy-eight were randomized to receive the mixture of diosmin, troxerutin, rutin, hesperidin, and quercetin (study group, SG), and 76 a mixture of diosmin in combination with hesperidin, diosmetin, isoroifolin, and linarin in purified micronized fraction (control group, CG). Bleeding, number of pathological piles, and Golligher's grade were assessed at each scheduled visit and compared using the Chi-square test. During the study period, bleeding improved after 1 and 6 months both in the SG (79.5 and 70.5%) and in the CG (80.2 and 75%) without significant differences between two groups. Satisfaction degree after 6 months was greater in the patients of the SG (4.05) towards the CG (3.25): this result was statistical significant (p 0.003).

Conclusions Use of flavonoids mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) is a safe and effective mean of managing bleeding from hemorrhoidal disease and minimal adverse events are reported.

Keywords Hemorrhoids · Therapy · Flavonoids · Anal bleeding

Introduction

Hemorrhoidal disease is one of the most common proctologic illnesses. This condition affects a large number of people in the world: the prevalence can vary from 4.4% in the general population to 36.4% in general practice [1]. It usually appears with symptoms and signs of bleeding, prolapse, soiling, itching, and pain. Bleeding is the most relevant and frequent symptom, reported by 56–81% of the patients; this sign is the most important reason for which most of patients are worried and they decide to be subjected to proctologic examination!

Medical and conservative management (life style changes, high-fiber diets, stool softeners, laxatives, and sitz baths) are treatments chosen in hemorrhoidal disease from Golligher's I to III degree [2].

Phlebotonics are heterogeneous and widely investigated classes of drugs used to treat hemorrhoidal disease, with the aim to obtain strengthening of blood vessel walls, increasing venous tone, lymphatic drainage, normalizing capillary permeability, and anti-inflammatory effects [3]. Flavonoids, including diosmin, hesperidin, and rutosides are the most

✉ Italo Corsale
itcorsal@hotmail.it

[1] General Surgery Unit, SS. Cosma e Damiano Hospital, Pescia, Italy

[2] General, Emergency and Mini-invasive surgery, Careggi University Hospital, Florence, Italy

[3] General Surgery Unit, Borgo San Lorenzo Hospital, Borgo San Lorenzo, Italy

[4] Unit of General Surgery 2, Policlinico Le Scotte, Siena, Italy

popular phlebotonics drugs; it seems that these ones, diosmin in combination with hesperidin, diosmetin, isoroifolin, and linarin in purified micronized fraction (PMFF), are able to obtain better results in current literature [4].

On the basis of these considerations, we thought it could be proper to carry out a randomized prospective double-blind investigation to evaluate how oral intake of new flavonoids mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) is effective in comparison with the oral intake of combination of PMFF to reduce bleeding from I–III degrees hemorrhoidal disease in the short and medium time.

Design and settings

Different patients both males and females showing I, II, or III degrees hemorrhoidal disease symptomatic for anal bleeding have been enrolled for this study. Patients were subjected to clinical evaluation in four different Italian colorectal units. Doctors' specialists of coloproctology were selected as participant investigators. The multicentric character of the study, with several provinces involved, contributes to the generalizability of the findings obtained. The study was conducted from January 2016 to December 2016. Exclusion criteria were allergy or intolerance to the flavonoids or any component of the medicaments, inflammatory bowel disease, obstructed defecation syndrome, pregnancy and puerperium, associated anal disease (abscess, fissure, fistula…) or hemorrhoidal thrombosis, proctologic surgical procedures (i.e., hemorrhoidectomy, stapled anopexy, fistula treatment…) within 1 year before recruitment, contemporary cancer or HIV, previous pelvic radiotherapy, patients receiving oral anticoagulant therapy, or contemporary administration of other therapy for hemorrhoidal disease. Patients with inability to understand the study or mental disorders were also excluded.

A list of opaque of progressively numbered envelopes containing instructions for the participation to the study, the dietary and igienic advice which must be followed and prescription for one of the therapies under evaluation, was generated with a computerized system for each center involved in the study. A closed envelope was given to every patient so that neither himself nor the physician knew the prescribed flavonoid (1° blind). Flavonoids administrated were Fleben® 1000 (diosmin 150 mg, troxerutin 300 mg, quercetin 150 mg, rutin 250 mg, and hesperidin 150 mg), one ampoule every 24 h for 20 days, and Daflon® (diosmin 450 mg in combination with hesperidin 50 mg in purified micronized flavonoid fraction), one tablet every 12 h for 20 days.

Supplementary dietary fibers have not been considered such exclusion criteria, but any contemporary topic therapy was not accepted. Patients were examined (clinical evaluation and proctoscopy) during the first month of the study, data were collected in a dedicated card; the investigator did not know which flavonoid was administrated to them. At the end of the observation period (6 months), the second clinical evaluation and proctoscopy was conducted and the envelope returned to the physician that only at this moment got to know the followed therapy (2° blind).

The primary outcome measure was the number of patients with no bleeding at first month. The second outcome measure was the number of patients in whom relapse of bleeding was prevented at 6 months. Severity of bleeding at defecation was defined like mild (in less than 50% of episodes), moderate (between 50 and 70% of episodes), or severe (over 70% of episodes). Moreover, the perceived bleeding from the patient was evaluated and detected by toilet paper or toilet. The variables included in the analysis were age, gender, pregnancies, number of pathological piles, and Golligher's grade of the hemorrhoidal disease. Adverse events were carefully registered. Severity of adverse events was classified into three levels: (I) mild, when no therapy was necessary; (II) moderate, when a specific treatment was needed; and (III) severe, when hospitalization was required, the reaction was life threatening, or contributed to the patient's death. Using a VAS scale (0 to 5), patients were questioned specifically about satisfaction degree on the administrated therapy.

Statistical analysis

The statistical analysis was carried out by using the Chi-square procedure (C). p values lower than 0.05 have been considered significant.

Results

Sixty-seven male and 87 female with median age 45.38 (range 21–74 years) consecutive patients with hemorrhoidal disease have been enrolled for this study. All patients were informed about the objectives of the study and invited to give their written informed consent to participate. Seventy-eight patients (32 male and 46 female), 45.05 years old (range 21–73) were treated with flavonoids mixture (diosmin 150 mg, troxerutin 300 mg, quercetin 150 mg, rutin 250 mg, and hesperidin 150 mg—Fleben® 1000) and assigned to the study group (SG). Seventy-six patients (35 male and 41 female), 45.42 years old (range 22–75) were treated with combination micronized diosmin and hesperidin (diosmin 450 mg in combination with hesperidin 50 mg in purified micronized flavonoid fraction—Daflon® 500) and assigned to the control group (CG). Details of groups are shown in Table 1.

Fifty-two vaginal deliveries were reported from 43 women in the SG and 48 vaginal deliveries were reported from 30 women in the CG. Slow transit constipation was detected in 26 (SG) and 27 (CG) patients. Anal bleeding was referred like mild in 28 patients in the SG and 21 in the CG, moderate from 25 (SG) and 33 (CG), and severe from 25 (SG) and 22 (CG), respectively.

Table 1 Baseline characteristics of patients

	Study group (%)		Control group (%)	
Patients	78		76	
Sex	32 M 46 F		35 M 41 F	
Age	45.05 (range 21–73)		45.42 (range 22–75)	
Vaginal delivery	52 in 43 women		48 in 30 women	
Slow transit constipation	26 (33.3)		27 (35.5)	
Bleeding	Mild	28 (36)	Mild	21 (27.7)
	Moderate	25 (32)	Moderate	33 (43.4)
	Severe	25 (32)	Severe	22 (28.9)
	Toilet paper	48 (61.5)	Toilet paper	32 (42)
	Toilet	30 (38.5)	Toilet	44 (58)
Time of bleeding	22.87 days		25.27 days	
Piles	1	19 (24.3)	1	13 (17)
	2	45 (57.7)	2	48 (64)
	3	12 (15.4)	3	15 (19)
	4	2 (2.6)	4	0
Golligher's degree	I	20 (25.6)	I	17 (22.4)
	II	40 (51.3)	II	36 (47.4)
	III	18 (23.1)	III	23 (30.2)

It was detected from 48 (SG) and 32 (CG) on the toilet paper, from 30 (SG) and 44 (CG) in the toilet. Bleeding had appeared from 22.87 days (range 4–38) in the SG and 25.27 days in the CG (range 6–39). Number of pathological piles find at clinical examination was one pile in 19 patients (SG) and 13 (CG), two piles in 45 (SG) and 48 (CG), three piles in 12 (SG) and 15 (CG), and four piles in 2 (SG), respectively. According to the Golligher's classification, in the SG 20 patients were classified as grade I disease, 40 patients' grade II disease and 18 patients' grade III disease. In the CG, 17 patients were affected from grade I disease, 36 patients from grade II disease, and 23 patients from grade III. There were no significant differences between the SG and CG at inclusion.

No subject was lost at follow-up for side effects or non-medical reasons; all patients completed the study. The reported side effects (five in the SG and six in the CG) were mild (I) gastrointestinal symptoms.

Clinical evaluation on the first month of the study 62 patients of the SG and 61 of the CG (79.5 vs 80.2%) reported absence of anal bleeding. However, seven (8.9%) patients in the SG and eight (10.5%) in the CG reported moderate or severe anal bleeding and four (5.13%) in the SG and six (7.9%) in the CG in the toilet. At proctoscopy analysis, we did not find pathological piles in 12 (15.4%) patients in the SG and 11 (14.5%) in the CG. One pile was found in 39 (SG) and 35 (CG) patients, 2 in 22 (SG) e 24 (CG), 3 in 3 (SG) e 6 (CG), and 4 in 2 (SG). There were no significant differences between the SG and CG at timeline I. Table 2 shows the results of the clinical evaluations at one month.

At timeline II (end of the study—6 months), complete response rate was about 70% in all subgroups. 55/78 (70.5%, SG) and 57/76 (75%, CG) patients did not report further anal bleeding (C 0.08—*p* 0.77—OR 1.11). Furthermore, anal bleeding was reported like mild from 15 patients (19.2%, SG) and 13 patients (17.1%, CG), while moderate or severe from 8 (10.2%, SG) and 6 (7.9%, CG) respectively. Blood was detected in the toilet on 8 patients both in the SG (10.2%) and in the CG (10.5%), on the toilet paper from 15 in the SG (19.2%) and 11 in the CG (14.5%). There were no significant differences between the SG and CG at proctoscopy control too (C 0.67—*p* 0.41—OR 0.69); we did not find pathological piles in 14 (17.9%) patients in the SG and 10 (13.2%) in the CG. One pile was found in 37 (SG) and 35 (CG) patients, 2 in 20 (SG) and 23 (CG), 3 in 5 (SG) and 8 (CG), and 4 in 2 (SG).

Satisfaction degree on the administrated therapy (VAS 0-5) was greater in the patients of the SG (4.05) than in the patients of the CG (3.25); this result was statistically significant (C 8.78—*p* 0.003—OR 0.72). Table 3 shows the results of the clinical evaluations at 6 months.

Discussion

Hemorrhoids are physiological structures known as vascular cushions and are found in the anal canal; their function is to ensure complete closure of the anus, especially to gas and liquid stools [5]. The exact pathophysiology of hemorrhoidal disease is still unclear. The theory that hemorrhoidal diseases develop

Table 2 Results at1 month—timeline I

		Total (%) 154	SG (%) 78	CG (%) 76	*p*
Bleeding	0	123 (79.9)	62 (79.5)	61 (80.2)	0.9 (*C* 0.01; OR 1.05)
	Mild	16 (10.3)	9 (11.5)	7 (9.2)	0.63 (*C* 0.22;OR 1.29)
	Moderate	9 (5.9)	3 (3.9)	6 (7.9)	0.28 (*C* 1.15;OR 0.47)
	Severe	6 (3.9)	4 (5.1)	2 (2.6)	0.42 (*C* 0.64;OR 2.00)
	Toilet paper	21 (13.6)	12 (15.4)	9 (11.8)	0.52 (*C* 0.41;OR 1.35)
	Toilet	10 (6.5)	4 (5.1)	6 (7.9)	0.48 (*C* 0.49;OR 0.63)
Piles	0	23 (14.9)	12 (15.4)	11 (14.5)	0.87 (*C* 0.03;OR 1.07)
	1	74 (48)	39 (50)	35 (46)	
	2	46 (29.9)	22 (28.2)	24 (31.6)	
	3	9 (5.9)	3 (3.8)	6 (7.9)	
	4	2 (1.3)	2 (2.6)	0	

C Chi square
OR odds ratio

because of varicose veins in the anal canal are obsolete [5] and has been replaced by the theory that progressive deterioration of the vascular cushions is responsible for hemorrhoidal illness [6]. In the "prolapse theory" A. Longo recently proposed that this progressive deterioration develops from a prolapse (anal or rectal), regarding the hemorrhoids like an iceberg's top [7]. Several studies have reported good symptomatic relief of the hemorrhoidal disease with phlebotonics although their precise mechanism of action has not been fully established and their effectiveness is a matter of discussed debate.

Alonso-Coello et al. [8] have reviewed 14 randomized trials, enrolling a total of 1514 participants, which compared the use of phlebotonics versus placebo or no treatment in hemorrhoidal disease. Several studies [9–11] have been reported the number of patients who had experience of bleeding as an outcome measure demonstrating the statistically significant beneficial effect of phlebotonics in treating symptomatic hemorrhoids (OR 0.12; 95% CI 0.04 to 0.37; $p = 0.0002$) with no statistical heterogeneity ($I2 = 0\%$). Despite the limit due to lack of homogeneity among the studies and different formatting of results, this meta-analysis has demonstrated a significant beneficial effect in using phlebotonics; anal bleeding was reduced in 67%, pain in 65%, and pruritus in 35% patients. A positive outcome with overall symptom improvement was assessed from several studies [12] proving a statistically significant beneficial effect by using phlebotonic medication (OR 15.99; 95% CI 5.97 to 42.84; $p < 0.00001$). Data also suggested benefits of phlebotonic treatment on the number of days to cessation of bleeding and mean number of days to cessation of bleeding [13]. Clinical practice guidelines [14] and technical reviews [15] have been less enthusiastic about the merits of flavonoids but still support their use.

Our study reports the therapeutic effectiveness of flavonoids mixture (diosmin 150 mg, troxerutin 300 mg, quercetin 150 mg,

Table 3 Results at 6 months—timeline II

		Total (%) 154	SG (%) 78	CG (%) 76	*p*
Bleeding	0	112 (72.7)	55 (70.6)	57 (75)	0.77 (*C* 0.08; OR 1.11)
	Mild	28 (18.2)	15 (19.2)	13 (17.2)	0.73 (*C* 0.12; OR 1.15)
	Moderate	8 (5.2)	5 (6.4)	3 (3.9)	0.49 (*C* 0.47; OR 1.61)
	Severe	6 (3.9)	3 (3.8)	3 (3.9)	0.97 (*C* 0.0; OR 0.97)
	Toilet paper	27 (17.53)	15 (19.2)	11 (14.5)	0.43 (*C* 0.62; OR 1.41)
	Toilet	16 (10.38)	8 (10.2)	8 (10.5)	0.95 (*C* 0.0; OR 0.97)
Piles	0	24 (15.7)	14 (17.9)	10 (13.2)	0.41 (*C* 0.67; OR 0.69)
	1	72 (46.7)	37 (47.4)	35 (46.1)	
	2	43 (27.9)	20 (25.7)	23 (30.2)	
	3	13 (8.4)	5 (6.4)	8 (10.5)	
	4	2 (1.3)	2 (2.6)	0	
VAS scale	Total		351	247	0.003 (*C* 8.78; OR 0.72)
	Average		4.05	3.25	

C Chi square
OR odds ratio

rutin 250 mg, and hesperidin 150 mg—Fleben® 1000) in relief anal bleeding from hemorrhoidal I to III degree diseases; we have compared this to a well-tested flavonoid (PMFF) rate than a placebo, due to ethical considerations, since it is not acceptable to exclude patients from an accepted therapy. In current literature, PMFF has been shown to reduce severity of bleeding [16] and prevent its relapse [17–19]. Our study confirms these results and 80.2% at 1 month and 75% at 6 months in CG did not report anal bleeding. Instead, just 79.5% at 1 month, and 70.6% at 6 months in the SG did not report anal bleeding; this result does not appear statistical differences between the SG and CG.

This analysis confirms that there is a potential benefit in using PMFF for hemorrhoidal anal bleeding, improving in over 75% of patients at 6 months. Patients with I to III degree hemorrhoids and anal bleeding can obtain good relief when treated with flavonoids mixture (diosmin 150 mg, troxerutin 300 mg, quercetin 150 mg, rutin 250 mg, and hesperidin 150 mg—Fleben®1000); absence of anal bleeding was reported from 79.5% at time line I (1 month) and 70.5% at timeline II (6 months) and no statistical differences in symptoms relief among two evaluated groups have been assessed.

Flavonoids mixture and PMFF have shown to be effective in improving the proctoscopy appearance of hemorrhoids both in the CG and SG, like assessed in current literature [20, 21], without statistical differences at 1 month (p 0.87) and 6 months (p 0.41) among two groups. However, the best satisfaction degree for the SG, maybe related to the administration (one ampoule every 24 h), is an interesting result with a potential impact on patients' quality of life and probably influencing the needs to return as soon as possible to their normal daily routine. Adherences to therapies is a primary determinant of treatment success and non-adherence can also occur when the medication regimen is complex (improper timing of drug administration, or administration of numerous medications at frequent or unusual times during the day) [22]. In a large systematic review of 76 trials, Claxton [23] found that adherence was inversely proportional to frequency of dose.

Simplify medication taking, using the most possible simplified regimen based on patient characteristics at the first level of drug use, is the key to improve patient's adherence to their prescribed treatment [24]. In accordance with Osterberg [25], we retain that simple dosing (one pill, once daily) helps to maximize adherence to therapy.

The study was well performed, without deviations and with minimal dropouts. This was facilitated by the fact that treatment was short lasting, simple, and inclusion could be completed easily.

Conclusions

Our results and analysis of the literature [26] indicate that flavonoids mixture (diosmin 150 mg, troxerutin 300 mg, quercetin 150 mg, rutin 250 mg, and hesperidin 150 mg—Fleben 1000) is safe and tolerable. The adverse events reported were minimal. Moreover, there were no acute (thrombosis) complications in the SG and CG. Further, pharmacosurveillance of the use of this product in actual clinical practice should confirm its effectiveness and explore its use in other clinical settings in order to optimize the cost-benefit ratio.

Despite the adequate safety profile, actually, we have not evidences that can suggest its administration during pregnancy; data examining their role in pregnant women are very limited and we cannot exclude possible teratogenic effects of flavonoids.

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