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ORIGINAL ARTICLE

Flavonoids mixture (diosmin, troxerutin, hesperidin) in the treatment of acute hemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial

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Abstract
Background The role of a mixture of phlebotonics in the treatment of acute hemorrhoid crisis is investigated to test their efficacy.
Methods One hundred and thirty-four consecutive patients with an acute hemorrhoidal crisis recruited in five colorectal units entered the study. Sixty-six of them were randomized to receive a mixture of diosmin, troxerutin and hesperidin (group A), and 68 a placebo (group B). The main symptoms, the use of oral painkillers and the Bristol scale score were recorded at each scheduled visit and compared using both Student's *t* test for independent samples and the ANOVA models for repeated measures. The presence of edema, prolapse and thrombosis were also recorded and compared using the Chi-square test. Furthermore, the trend of proportions during the time of the evaluations was assessed by the Chi-square test for linear trend.
Results Pain, bleeding and the proportion of patients who reported persistence of edema and thrombosis decreased significantly after 12 days of treatment in group A. After 6 days, the number of paracetamol tablets taken by patients in group A was significantly lower than the amount of flavonoid mixture.
Conclusions The use of a mixture of diosmin, troxerutin and hesperidin is a safe and effective mean of managing symptoms of acute hemorrhoidal disease. Furthermore, in patients receiving treatment, there was faster control and lower persistence of edema and thrombosis.

Keywords Hemorrhoidal crisis · Flavonoids · Anal pain · Anal bleeding · Anal itching

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Introduction

Hemorrhoidal disease is the commonest proctologic condition in the general population particularly among individuals of higher socioeconomic status, pregnant women and constipated patients [1]. The prevalence reported by a recent Cochrane review ranges between 4.4 % in the general population and 36.4 % in general practice [2].

The acute clinical manifestation of hemorrhoidal disease is characterized by pain, bleeding, itching, prolapse, edema and often thrombosis. This is commonly known as "hemorrhoidal crisis."

Noninvasive treatment of the acute crisis could make it possible to avoid invasive procedures or postpone them to a more convenient time when edema, pain and thrombosis have regressed, allowing a more correct staging of the disease, in order to plan the most appropriate therapeutic approach.

Conservative treatment of hemorrhoids is indicated for grade I or grade II hemorrhoids and is based on diet and lifestyle modification, adequate fiber intake and phlebotonics as recommended by several national and international guidelines [3, 4] since regular bowel activity, easy defecation and vasoactive medications can prevent hemorrhoidal prolapse and minimize bleeding [1]. On the other hand, more advanced grades of hemorrhoids (III–IV) should be treated surgically [2].

Although the efficacy of flavonoids in the treatment of hemorrhoids is still a matter of debate, several trials, reviews and meta-analyses have demonstrated their role in prevention and control of hemorrhoid symptoms [2, 5, 6]. The mechanism of action of flavonoids on hemorrhoid symptoms is still not completely known, but they seem to act by improving venous tone, reducing capillary permeability, increasing lymphatic drainage and an anti-inflammatory effect [7–11]. However, the role of flavonoids in the treatment of acute hemorrhoidal crisis has never been clarified and the utility of phlebotonics in the acute phase is viewed with some skepticism by proctologists. The aim of this trial was to assess the efficacy of the oral intake of a mixture of diosmin, troxerutin and hesperidin (Triade H®, Omikron Italia Srl) in improving symptoms of patients with acute hemorrhoidal crisis in a randomized, controlled, triple-blind trial.

Materials and methods

Patients and study design

All consecutive patients, of both sexes, between 18 and 75 years of age, with acute hemorrhoidal crisis, evaluated in five Italian colorectal units between September 2013 and June 2014, entered the study after a written informed consent was obtained. Acute hemorrhoidal crisis was defined as acute anal pain due to engorged hemorrhoidal prolapse with or without bleeding, edema and thrombosis.

Exclusion criteria were colon, rectal or anal cancer, anticoagulant treatment or coagulation disorders, anal abscess or fistula, anal fissure, pregnancy, inflammatory bowel disease, metabolic or endocrine disorders, previous anorectal surgery and/or radiotherapy to the pelvi-perineal region, as well as known allergy or intolerance to flavonoids.

The study population was randomized into two arms: group A (Triade H®, Omikron Italia Srl, Rome, Italy) and group B (placebo) using random permuted blocks of 30 sealed envelopes containing the chosen treatment (A or B). The progressively numbered closed envelopes were assigned to each unit involved in the study together with the exact number of sachets and tablets scheduled for the full treatment. The physician and the patients were blinded to the randomization code, and the data were blindly analyzed by the statistician unaware of the assigned treatment.

The study was approved by the local ethics committee, and the CONsolidated Standard of Reporting Trials checklist and flow diagram were used (Fig. 1).

Both groups received topical emollient ointment (chosen by each unit) free from cortisone and/or local anesthetics and general recommendations to facilitate easy evacuation using stool softeners.

The treatment started immediately after the diagnosis was made and informed consent was obtained, and consisted of the oral intake of one sachet of the powder diluted in half glass of water three times daily for 3 days, and then one sachet twice daily for 2 days and one sachet once a day for another 7 days. Starting from the 13th day, the treatment was switched from sachets to tablets and one tablet was administered daily for a month. Oral painkillers (500 mg paracetamol) were used if necessary, and their use recorded.

The active drug tested (Triade H®) was a mixture of diosmin, troxerutin and hesperidin, which have documented effects on the microcirculation and bleeding due to their antioxidant, anti-inflammatory and phlebotonic action [8, 9]. The sachets given to patients contained 300 mg of each flavonoid plus vitamin C (12 mg) and excipients, whereas the tablets contained diosmin 300 mg, troxerutin 300 mg, hesperidin 100 mg plus excipients.

The tablets and the powder with active drugs were made macroscopically indistinguishable from the placebo, which contained only the excipients. The study plan included five visits (V1 patients' recruitment–V5 last follow-up) in order to assess the efficacy of the treatment. At visit V1, after receiving written informed consent, clinical data and proctologic evaluation were carried out to ascertain the fulfillment of the entry criteria. Furthermore, the clinical data (including anal pain, bleeding, itching, bowel habits) and proctologic evaluation (including the presence of prolapse, edema and thrombosis) were recorded at each scheduled visit.

Visit V2 was scheduled at day 4°, V3 at day 6°, V4 at day 12° and V5 at the end of treatment (the 42nd day from recruitment).

At each visit patients were asked to self-assess the main symptoms (pain, bleeding and itching) using a 10-cm continuous linear visual analogue scale (VAS), while the presence of edema, prolapse and thrombosis was evaluated and recorded by the physician (and scored as present/absent). The number of painkiller tablets taken was also recorded. Furthermore, at V5, the persistence of hemorrhoidal crisis was evaluated.

The safety of the treatment was also assessed by recording side effects requiring suspension or changes in the therapy. Finally, the Bristol Stool Form (BSF) scale score was recorded to define the characteristics of the patients' stools and evaluate any effects of bowel habits on outcome.

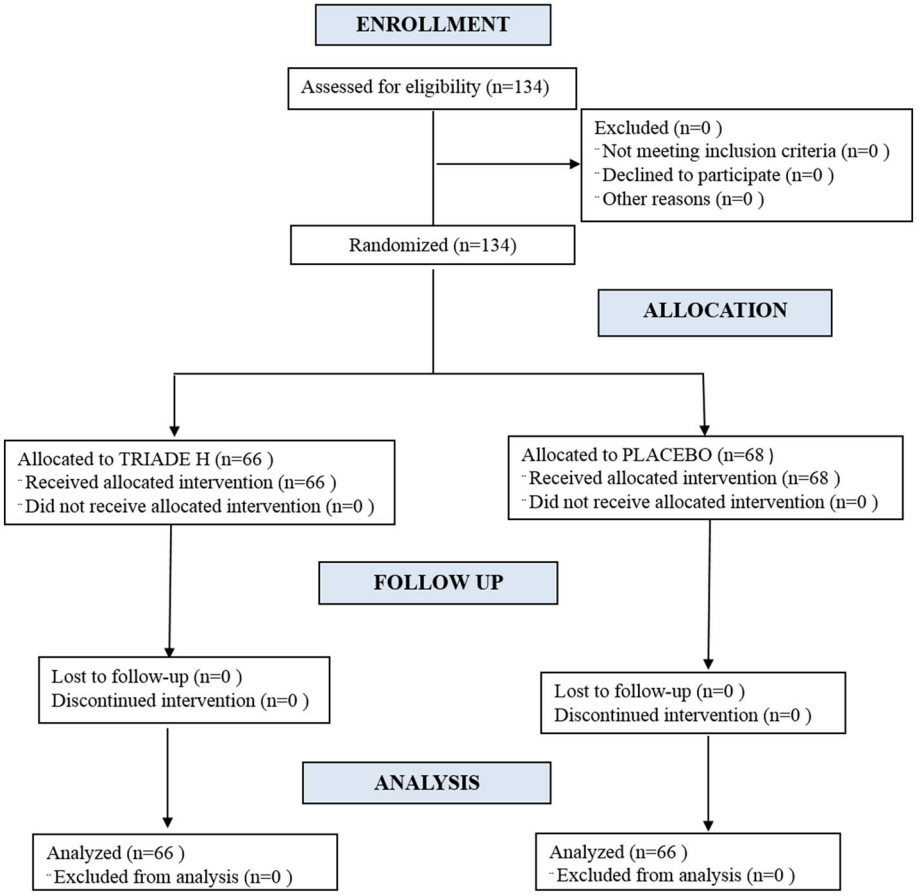

Fig. 1 CONsolidated Standard of Reporting Trials flow diagram

Sample size calculation and study power

Given an α error of 5 % and a β error of 20 %, the expected number of patients in each arm of the study to detect a 20 % increase in the number of positive response to the treatment compared to the placebo is 60. The calculated power of the study is 92 % with a confidence interval of 95 % (reference: Power and Precision software Biostat Englewood, NJ 07631, USA). With a possible 10 % dropout rate, 132 patients were scheduled to complete the study.

Statistical analysis

The coordinator unit collected an Excel spreadsheet containing all the data recorded from each unit participating the study. The randomization code was opened at the time of data analysis and results were analyzed by STATA MP 11® statistical software.

The proportion of patients in which the VAS values decreased from V1 to V5 (number of positive response to the treatment compared to the placebo) was calculated using the Chi-square test.

The VAS values of each main symptom, the number of paracetamol tablets and the Bristol scale scores were expressed as mean ± standard deviation (SD); means in two groups were compared for each scheduled visit (V1–V5) using Student's *t* test for independent samples. In order to study the differences in the means between two groups and the role of time, analysis of variance (ANOVA) models for repeated measures were set. The presence of edema, prolapse and thrombosis was described as a proportion that was compared using the Chi-square test. Furthermore, the trend of proportions during the time of the evaluations was assessed by the Chi-square test for linear trend. A p value <0.05 was considered significant.

Results

Overall, 134 patients (male-to-female ratio (M/F) = 1:1) with an average age of 48.7 ± 12.9 years (range 19–73 years) were prospectively recruited. Sixty-six patients ($M/F = 1.27$; mean age 48 ± 11.9 years) were randomized to receive Triade H® treatment (group A), and 68 patients ($M/F = 1.19$; mean age 49.3 ± 14.4 years) to receive placebo (group B). No significant differences in the

Table 1 Preoperative demographic characteristics

	Triade H® group	Placebo group	*P* value
Total number of patients	66 (49.3 %)	68 (50.7 %)	–
Males/females	37/29	37/31	0.225
Mean age (years, SD)	48 ± 11.9	49.3 ± 14.4	0.28

SD Standard deviation

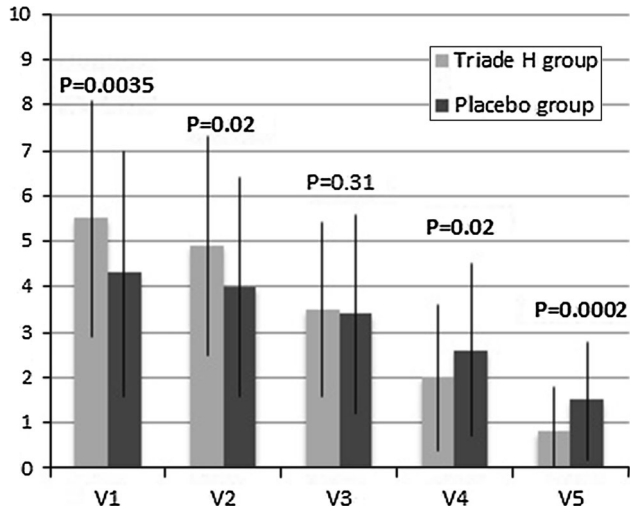

Fig. 2 Mean visual analogue scale score for pain at each scheduled visit

distribution of sex ($p = 0.225$) or age ($p = 0.28$) were recorded between the two groups (Table 1), and there were no differences in their bowel habits at any time during the study when evaluated by the BSF scale ($p = 0.29$ at V1; $p = 0.20$ at V2; $p = 0.30$ at V3; $p = 0.24$ at V4 and $p = 0.06$ at V5).

There were no dropouts. All patients recruited completed the study without relevant side effects.

The comparison of the VAS scores over the time V1–V5 showed a statistical significant difference between the two groups: 58/66 patients in group A experienced progressive pain reduction during treatment versus 38/68 in group B (Chi-square = 16.9; $p < 0.0001$); bleeding decreased over time in 42/66 patients in group A and in 29/68 patients in group B (Chi-square = 5.9; $p = 0.015$); anal itching decreased from V1 to V5 in 37/66 patients in group A and in 22/68 patients in group B (Chi-square = 7.63; $p = 0.006$).

The mean VAS score for pain at V1 (before starting treatment) was significantly higher in group A and remained higher at V2. However, at V3, the difference in the pain scores was not significant and, at V4 and V5, the pain score decreased significantly in group A (Fig. 2; Table 2).

Table 2 Mean visual analogue scale score for pain at each scheduled visit (mean, standard deviation)

Scheduled visits	Overall (134 patients)	Triade H® group (66 patients)	Placebo group (68 patients)	*t*	*P* value
V1	4.9 ± 2.7	5.5 ± 2.6	4.3 ± 2.7	2.7	0.0035
V2	4.4 ± 2.4	4.9 ± 2.4	4.0 ± 2.4	1.9	0.02
V3	3.4 ± 2.1	3.5 ± 1.9	3.4 ± 2.2	0.5	0.31
V4	2.3 ± 1.8	2.0 ± 1.6	2.6 ± 1.9	1.9	0.02
V5	1.1 ± 1.2	0.8 ± 1.0	1.5 ± 1.3	3.6	0.0002

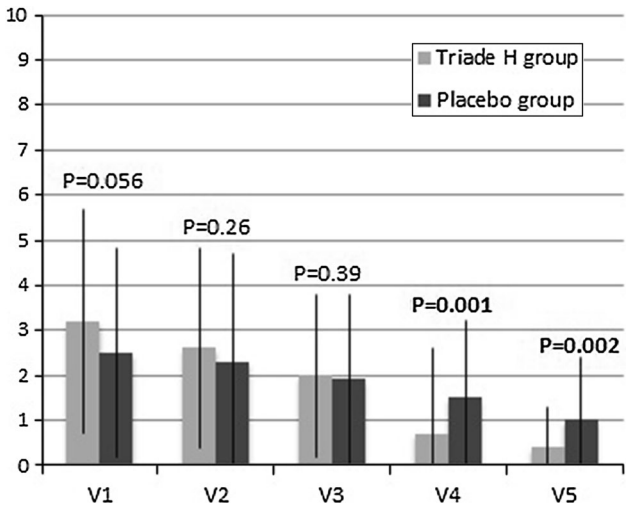

Fig. 3 Mean visual analogue scale score for bleeding at each scheduled visit

Table 3 Mean visual analogue scale score for bleeding at each scheduled visit (mean, standard deviation)

Scheduled visits	Overall (134 patients)	Triade H® group (66 patients)	Placebo group (68 patients)	*t*	*p* value
V1	2.9 ± 2.4	3.2 ± 2.5	2.5 ± 2.3	1.6	0.056
V2	2.5 ± 2.3	2.6 ± 2.2	2.3 ± 2.4	0.6	0.26
V3	2.0 ± 1.8	2.0 ± 1.8	1.9 ± 1.9	0.3	0.39
V4	1.1 ± 1.5	0.7 ± 1.1	1.5 ± 1.7	3.0	0.001
V5	0.7 ± 1.2	0.4 ± 0.9	1.0 ± 1.4	2.8	0.0027

Although the ANOVA models showed a significant reduction in VAS scores over time in both groups ($F = 222.9$; $p < 0.0001$), a significant interaction between time and active treatment was seen ($F = 17.7$; $p < 0.0001$).

The mean VAS score for bleeding did not show any difference between the two groups at V1 and V2, but at V4 and V5, the average values were higher in the placebo group ($p = 0.001$ and $p = 0.0027$, respectively) (Fig. 3; Table 3).

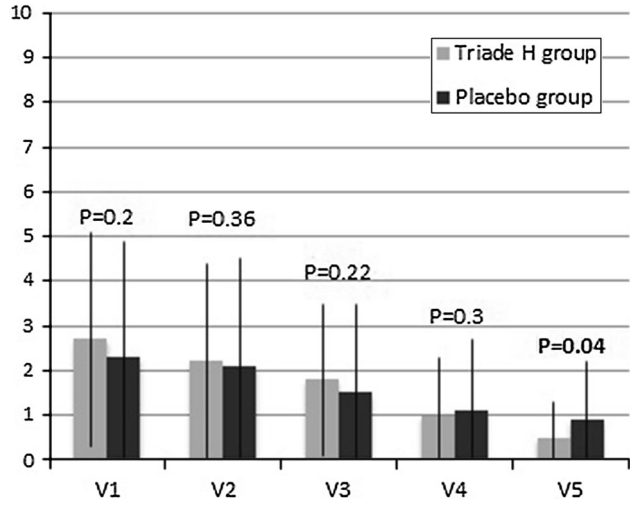

Fig. 4 Mean visual analogue scale score for itching at each scheduled visit

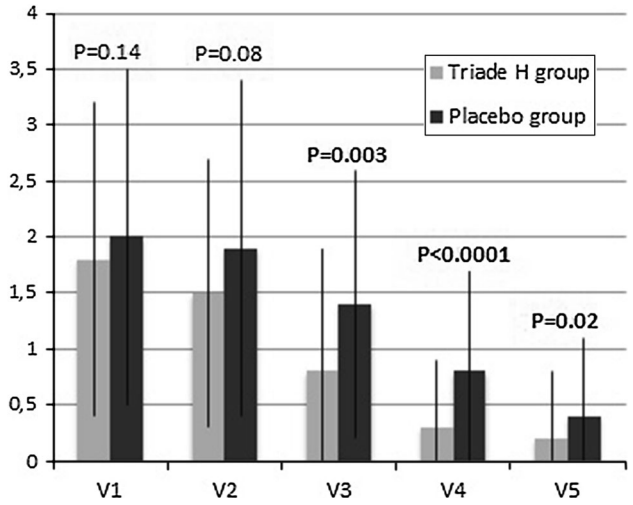

Fig. 5 Number of painkiller tablets reported at each scheduled visit

Table 4 Mean visual analogue scale score for anal itching at each scheduled visit (mean, standard deviation)

Scheduled visits	Overall (134 patients)	Triade H® group (66 patients)	Placebo group (68 patients)	*t*	*p* value
V1	2.5 ± 2.5	2.7 ± 2.4	2.3 ± 2.6	0.8	0.20
V2	2.2 ± 2.3	2.2 ± 2.2	2.1 ± 2.4	0.3	0.36
V3	1.6 ± 1.8	1.8 ± 1.7	1.5 ± 2.0	0.8	0.22
V4	1.1 ± 1.5	1.0 ± 1.3	1.1 ± 1.6	0.5	0.30
V5	0.7 ± 1.1	0.5 ± 0.8	0.9 ± 1.3	1.7	0.041

Table 5 Mean number of painkiller tablets recorded at each scheduled visit (mean, standard deviation)

Scheduled visits	Overall (134 patients)	Triade H® (66 patients)	Placebo (68 patients)	*t*	*p* value
V1	1.9 ± 1.4	1.8 ± 1.4	2.0 ± 1.5	1.1	0.14
V2	1.7 ± 1.3	1.5 ± 1.2	1.9 ± 1.5	1.4	0.08
V3	1.1 ± 1.2	0.8 ± 1.1	1.4 ± 1.2	2.7	0.003
V4	0.6 ± 0.8	0.3 ± 0.6	0.8 ± 0.9	4.1	<0.0001
V5	0.3 ± 0.6	0.2 ± 0.6	0.4 ± 0.7	2.1	0.02

The ANOVA models showed a significant reduction in the VAS score for bleeding over time in both groups ($F = 100.4$; $p < 0.0001$), and a significant interaction between time and active treatment was seen ($F = 11.0$; $p < 0.0001$).

No difference in the mean VAS score for anal itching was noted between the two groups at V1–V4; however, at V5, the mean anal itching score was significantly lower in group A ($p = 0.04$) (Fig. 4; Table 4). In both groups, however, a positive trend for anal itching improvement over time ($F = 2.3$; $p = 0.05$) and between time and active treatment was observed ($F = 2.3$; $p = 0.05$).

The number of paracetamol tablets taken was significantly lower in group A compared to placebo at V3, V4 and V5 ($p = 0.003$, $p < 0.0001$ and $p = 0.02$, respectively) (Fig. 5; Table 5) and in both groups decreased significantly over time ($F = 108.9$; $p < 0.0001$). For painkiller intake, no interaction between time and active treatment was recorded ($F = 1.32$; $p = 0.25$).

The Chi-square test for linear trends showed a significant reduction in edema over time in both groups (Chi-square = 9.92; $p = 0.0016$), but the proportion of patients who reported occurrence and persistence of edema was lower in group A at V4 ($p = 0.011$) and V5 ($p = 0.018$) (Fig. 6; Table 6).

No significant differences were noted regarding the occurrence of hemorrhoidal prolapse at any time or over time (Chi-square = 2.78; $p = 0.09$) (Fig. 7; Table 7).

Although the Chi-square test for linear trends showed a significant reduction in thrombosis over time in both groups (Chi-square = 5.63; $p = 0.02$), the proportion of patients who reported thrombosis was significantly lower in group A at V4 ($p < 0.0001$) (Fig. 8; Table 8).

Discussion

Hemorrhoidal disease is characterized by dilatation and engorgement of the hemorrhoidal plexuses, disruption of supporting connective tissue, inflammatory reaction and vascular hyperplasia [12].

The utility of phlebotonics has been widely stressed in the treatment of chronic venous insufficiency [13–18] and,

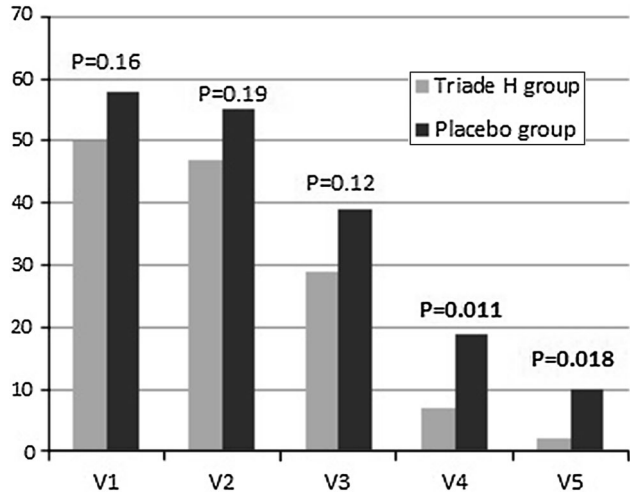

Fig. 6 Number of patients with edema at each scheduled visit

Table 6 Proportion of patients with edema at each scheduled visit

Scheduled visits	Overall (134 patients)	Triade H® (66 patients)	Placebo (68 patients)	Chi-square	*p* value
V1	108	50	58	1.9	0.16
V2	102	47	55	1.7	0.19
V3	68	29	39	2.4	0.12
V4	26	7	19	6.4	0.011
V5	12	2	10	5.6	0.018

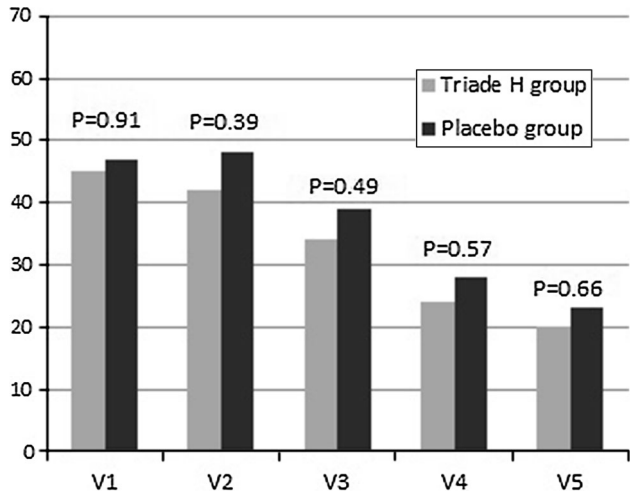

Fig. 7 Number of patients with prolapse at each scheduled visit

although their efficacy in treating of hemorrhoids is still a matter of debate, their use is reported to improve clinical symptoms by reducing vascular congestion, increasing venous tone, lymphatic drainage and controlling the inflammation of the microcirculation [7–9]. Their mechanism of action is not completely understood; however, a strong

Table 7 Proportion of patients with prolapse at each scheduled visit

Scheduled visits	Overall (134 patients)	Triade H® (66 patients)	Placebo (68 patients)	Chi-square	*p* value
V1	92	45	47	0.014	0.91
V2	90	42	48	0.73	0.39
V3	73	34	39	0.46	0.49
V4	52	24	28	0.32	0.57
V5	43	20	23	0.19	0.66

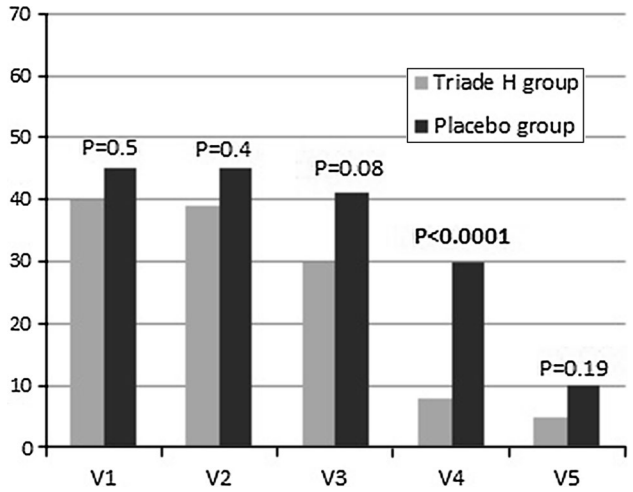

Fig. 8 Number of patients with thrombosis at each scheduled visit

Table 8 Proportion of patients with thrombosis at each scheduled visit

Scheduled visits	Overall (134 patients)	Triade H®(66 patients)	Placebo (68 patients)	Chi-square	*p* value
V1	85	40	45	0.45	0.50
V2	85	39	45	0.72	0.40
V3	71	30	41	2.96	0.085
V4	38	8	30	16.9	<0.0001
V5	15	5	10	1.71	0.19

scavenger of the hydroxyl radicals has been reported which improves microcirculation [1].

This randomized, triple-blind study has demonstrated that the mixture of flavonoids tested has significant effects on the main symptoms of hemorrhoidal crisis causing a significant and rapid reduction in anal pain and bleeding compared to placebo. Furthermore, objective clinical evaluation of edema and thrombosis showed that both were significantly reduced in the two groups over time, but that

in the patients treated with the active drugs, improvement was more rapid and more consistent, as reflected in the changes in symptoms.

In particular, although anal pain and bleeding were significantly worse in group A at the time of recruitment and randomization (V1), improvement in these symptoms was significantly faster in this group compared to placebo.

There was no statistically significant difference in anal itching between the two groups at any time except at the end of treatment, after 42 days, (V5) which indicates the utility of prolonged treatment.

Prolapse is due to a sliding of the hemorrhoidal cushions due to damage of the supporting connective tissue, and no pharmacological treatment is currently expected to reduce the extracellular matrix degradation accounting for this sliding.

The intake of painkiller tablets was significantly lower after day 6 of treatment in group A compared to placebo, and the persistence of edema and thrombosis was also lower in group A although stool consistency, evaluated by means of the BSF scale, did not differ significantly between the two groups.

Our findings are partially supported by the literature. In fact, a recent Cochrane review and a recent meta-analysis favor the use of phlebotonics to improve symptoms (particularly anal bleeding) and reduce recurrence [2, 19]. Furthermore, one of the most commonly investigated flavonoids, the micronized purified flavonoid fraction, consisting of 90 % diosmin and 10 % hesperidin, (two of the components of Triade H®), has been reported to reduce rectal discomfort, pain and bleeding in the conservative management of hemorrhoids and even after open hemorrhoidectomy [19, 20].

Conclusions

Our randomized study demonstrates that the use of a mixture of diosmin, troxerutin and hesperidin in patients with acute hemorrhoidal disease is safe and could significantly help to manage typical symptoms. Although the analysis of the data highlighted a tendency for symptoms improvement over time in both groups, in patients receiving Triade H®, there were faster control and less persistence of symptoms, edema and thrombosis.

Conflict of interest *Omikron Italia Srl* has been involved in the study by generously providing the active drug and placebo to the units, but did not have access to the data either in the recruitment or in the elaboration and interpretation of the data.

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