Original article

Clinical effectiveness of a highly standardized and bioavailable mixture of flavonoids and triterpenes in the management of acute hemorroidal crisis

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Abstract. *Background and aim of the work*: Patients with acute haemorrhoidal crisis often need of an immediate and effective pharmacological approach to alleviate their pain, bleeding and swelling or have to be referred by the general practitioner to the surgeon for a definitive treatment. Effective and not invasive treatment control of the acute crisis could be of practical use in order to avoid or to delay invasive procedures to a time more convenient for the patient and/or for the surgeon. *Methods*: After enrolling, according to the group treatment, every patient starts taking 1 tablet every 8 hours for 7 days of Emospid® or 2 tablets every 8 hours for 7 days of MMDH tablets. According to a simplified PATE 2000 classification, the following parameters were evaluated: haemorrhoidal grade, internal and external haemorrhoids, internal and external oedema, internal and external thrombosis, bleeding, bleeding intensity, pain, itching, defecation problems and urgency, tenesm, mucus in stools and sphinterial tone. *Results*: In the Emospid® group, within the considered period, 35 patients out 40 shift downwards of 1 grade of the haemorrhoidal scale (from III to II and from II to I); 22 out of 29 stop bleeding; bleeding intensity drops by about 90%; pain ceased in 33 out of 38; pain intensity drops by about 75%; itching ceased in 25 out 35; tenesm ceased in 32 out of 33; sphinterial tone reduced from hypertonic to normal in 19 out 24; mucus in the stools was found in 3 out of 12; 12 out 35 still presented defecation disorders; defecation urgency was found in 2 out of 14; need to defecate in 2 times was found in 1 out of 17; acute events (external and/or internal oedema, external and/or internal thrombosis) was found in 10 out of 36. In the MDHH group results were, in terms of global evaluation, inferior of about 25-50% according to the considered parameter when compared with the one got by the Emospid® treatment. *Conclusions*: Patients with acute haemorrhoidal crisis may be successfully treated with Emospid® in order to avoid or to delay, if acute crisis relapsed, invasive procedures. Moreover, the treatment with Emospid® shows to be more effective, if compared with MMDH, in counteracting acute haemorrhoidal crisis. (www.actabiomedica.it)

Key words: haemorrhoids; acute; crisis; OPC, anthocyanosides, CAST, diosmin, hesperidin

Introduction

The acute stage of haemorrhoidal disease, called haemorrhoidal crisis, presents with severely disabling, irreducibly prolapsed or gangrenous haemorrhoids (1). Most of these patients have had longstanding haemorrhoidal disease of variable severity. The crisis is characterized by acute pain, bleeding, inflammation, a foul-smelling discharge and circumferentially irreducible haemorrhoids. It occurs because the anal sphincter squeezes and strangles the prolapsed internal haemorrhoids. The result of sphincter spasm and

blockade of venous return causes oedema and, occasionally, thrombosis of the external haemorrhoids. The resulting pain, swelling and disability are dramatic and very painful (2). Haemorrhoidal crisis is not infrequent and it usually requires emergency medical treatment. Non-operative treatments (e.g. analgesics, stool softeners, local ointment, suppositories and manual reduction) have been considered as a safety option. However in some cases these may prolong disability. Moreover, such patients may need subsequent re-hospitalization for surgery (3). Other non-operative approach is the oral use of flavonoids. Often called "bioflavonoids", these are colourful substances that widely occur in the Plant Kingdom. Reasonably good, though not indisputable, evidence suggests that these bioflavonoids may be helpful for haemorrhoids. Many studies describe OPC from grape seeds, anthocyanosides from bilberry and diosmin and hesperidin from citrus to be valid tools especially for treating chronic haemorrhoids (4). Some papers describe a micronized mixture of diosmin (90%) and hesperidin (10%) to be also effective in acute haemorrhoidal crisis especially in reducing severity of bleeding (5, 6). Due to the likely poor oral bioavailability of flavonoids (7), such mixture need to be used at least at 3000-4000 mg/die (6-8 tablets/die). On the contrary, other flavonoids show better kinetics and better oral bioavailability especially if complexed with lipophilic carriers (Phytosome®) (8). Their use allows to assume a better patient compliance. Recently a multi-layer tablets (Emospid®, PharmExtracta, Italy) has been developed by using Phytosome® and sustained-release technologies with the aim of optimizing oral bioavailability of its active constituents (OPC, anthocyanosides, CAST). We have then decided to compare the clinical efficacy of the micronized mixture of diosmin and hesperidin (MMDH) with the one of Emospid® in patients during an acute haemorrhoidal crisis.

Materials and methods

Patients

The institutional ethics committee of University of Perugia approved the study protocol. Patients were enrolled by the Phlebology Department of the same University. After giving written informed consent, eligible patients were assessed at baseline for demographic characteristics; vegetarian or non-vegetarian diet; degree of haemorrhoids; associated diseases; blood pressure; blood analysis. They were then randomized to receive Emospid® or MMDH by a selection key: every 2 patients assigned to the Emospid® group, 1 patient was assigned to the MMDH one. At the end of the scheme 40 patients (19 males and 21 females) were treated with Emospid® and 20 pts. (10 males and 10 females) were treated with MMDH.

Inclusion criteria

Inclusion criteria were diagnosis of acute hemorrhoidal crisis; presence of hemorrhoids of grade 2 (with bleeding and/or oedema), grade 3 or grade 4; age between 18 and 85 yrs.

Exclusion criteria

Exclusion criteria were age less than 18 or more than 85 yrs.; pregnancy; breastfeeding; diagnosis of cancer; diagnosis of inflammatory bowel disease (i.e. ulcerative rettocolitis, Crohn disease); liver pathology; heart pathology.

Treatment scheme and evaluation scheme

After enrolling, according to the group treatment, every patient starts taking 1 tablet every 8 hours for 7 days of Emospid® or 2 tablets every 8 hours for 7 days of MMDH tablets.

According to a simplified PATE 2000 classification, at baseline (t=1st day) and after 1 week (7th day) the following symptoms and parameters were evaluated: haemorrhoidal grade, internal and external haemorrhoids, internal and external oedema, internal and external thrombosis, bleeding, bleeding intensity (by a visual analogical scale from 0 to 3 corresponding to: no bleeding; occasional, moderate, abundant); pain; spontaneous pain intensity; intensity of pain during evacuation (pain intensity was evaluated by a visual analogical scale ranging from 0, absent, to 10, unbear-

able); itching, defecation problems; defecation urgency; defecation splitted in 2 times; tenesm; presence of mucus in stools; sphinterial tone.

Tablets content

Emospid®, traded in Italy by PharmExtracta, Pontenure (PC), Italy, is a 3-layered tablet containing in the upper (30/45 minutes-releasing) layer 100 mg of Leucoselect Phytosome®, in the middle (8 hour sustained-releasing) layer 30 mg of *Centella Asiatica* Selected Triterpenes (CAST) and in the lower (30/45 minutes-releasing) layer 80 mg of Mirtoselect®. Leucoselect Phytosome® corresponds to a highly standardized mixtures of oligomeric procyanidines (OPC), extracted by the outer part of *Vitis vinifera* seeds, complexed with distearoylphosphatidilcholine from soy (*Glycine max*). CAST corresponds to a mixture of asiatic acid, madecassic acid and asiaticoside (ratio 30:30:40) extracted from the aerial parts of *Centella asiatica*. Mirtoselect® corresponds to a highly standardized mixture (titred as 36%) of anthocyanosides extracted from berries of *Vaccinium myrtillus*. The all 3 actives were provided by Indena SpA, Milan, Italy. Emospid® is currently manufactured by SIIT Srl, Trezzano S/N (MI), Italy.

MMDH tablets, traded in Italy as Daflon® (Servier) or Arvenum® (Stroder), are tablets containing a micronized mixture of 500 mg/tablet of diosmin and hesperidin in ratio of 90:10.

Statistical analysis

In order to evaluate groups homogeneity in terms of sex and age, the efficacy of the treatments and the relevance of side effects incidence, the Student's *t* test was used and $p < 0.05$ was considered to be statistically significant.

Results

As described in the Materials and Methods section, according to a protocol agreed with the Ethical Committee of the University of Perugia, 60 patients were enrolled after diagnosis of acute haemorrhoidal crisis and treated with either Emospid® or with MMDH, a micronized mixture of diosmin and hesperidin. Every treatment was given every 8 hours for 7 days, corresponding to 3 tablets/day for Emospid® and 6 tablets/day for MMDH.

Within the considered period (7 days) in the Emospid® group (n=40), 35 patients out of 40 shift downwards of 1 grade of the haemorrhoidal scale (from III to II and from II to I) while in the MMDH group (n=20) the event was observed in 10 out of 20 patients (Table 1). As regards to the number of subjects with bleeding, in the Emospid® group 22 out of 29 pts. stop bleeding while in the MMDH group this was observed in 8 out 14 patients (Table 2). In terms of bleeding intensity, the values (measured from 0 to 3 corresponding respectively from "no bleeding" to "abundant") drop by about 90% in the Emospid® group and by 84% in the MMDH group (Table 2). The pain (Table 3) ceased in 33 out of 38 pts. in the Emospid® group and in 13 out of 19 pts. in the MMDH group. Pain severity scores, spontaneous and during defecation, drop in both cases by about 75% in the Emospid® and by 62% and by 72% respectively in the MMDH group (table 4). As shown in Table 5, itching ceased in 25 out 35 pts. in the Emospid® group and in 10 out of 17 pts. in the MMDH group. As reported in Table 6, tenesm ceased in 32 out of 33 patients in the Emospid® group and in 15 out of 18 pts. in the MMDH group.

As regards to the sphinterial tone (Table 7) it was reduced from hypertonic to normal in 19 out of 24 pts. in the Emospid® group and in 8 out of 13 pts. in the MMDH. Mucus in the stools (Table 8) was found on-

Table 1. Number of subjects and relative haemorrhoidal grade (from 1 to 4) at baseline and after 7 days of treatment

Product	n	baseline				7th day			
		I	II	III	IV	I	II	III	IV
Emospid®	40	0	19	19	2	18*	18	2*	2
MMDH	20	0	9	10	1	6°	7	6°	1

* p<0.01; ° p<0.05 (versus baseline value)

Table 2. Number of subjects with bleeding and bleeding severity score^ at baseline and after 7 days of treatment

Product	n	baseline	7th day	baseline score	7th day score
Emospid®	40	29	7*	1.84±0.33	0.17±0.03*
MMDH	20	14	6°	1.59±0.25	0.25±0.07*

^ by a visual analogical scale from 0 to 3 corresponding to: no bleeding (0); occasional (1), moderate (2), abundant (3).
* p<0.01; ° p<0.05 (versus baseline value)

Table 3. Number of subjects with pain at baseline and after 7 days of treatment

Product	n	baseline	7th day
Emospid®	40	38	5*
MMDH	20	19	6°

* p<0.01; ° p<0.05 (versus baseline value)

Table 4. Pain severity score^ (spontaneous=S and during defecation=DD) at baseline and after 7 days of treatment

Product	S baseline score	S 7th day score	DD baseline score	DD 7th day score
Emospid®	6.10±2.30	1.40±0.50*	7.30±2.50	1.70±0.40*
MMDH	6.30±2.40	1.90±0.70*	7.50±2.20	2.10±0.60°

^ pain intensity was evaluated by a visual analogical scale ranging from 0, absent, to 10, unbearable
* p<0.01; ° p<0.05 (versus baseline value)

Table 5. Number of subjects with itching at baseline and after 7 days of treatment

Product	n	baseline	7th day
Emospid®	40	35	10*
MMDH	20	17	7°

* p<0.01; ° p<0.05 (versus baseline value)

Table 6. Number of subjects with tenesm at baseline and after 7 days of treatment

Product	n	baseline	7th day
Emospid®	40	33	1*
MMDH	20	18	3*

** p<0.01 (versus baseline value)*

ly in 3 out of 12 patients in the Emospid® group and in 3 out of 7 pts. in the MMDH group. As shown in Table 9, 12 out of 35 pts. of the Emospid® group presented defecation disorders, the same occurred in 8 out of 17 pts. in the MMDH group.

Table 7. Number of subjects and relative sphinterial tone^ at baseline and after 7 days of treatment

Product	n	baseline			7th day		
		h	N	H	h	N	H
Emospid®	40	0	16	24	0	35°	5*
MMDH	20	0	7	13	0	15	5°

^sphinterial tone has been classified as hypotonic (h), normal (N) and hypertonic (H)
* p<0.01; ° p<0.05 (versus baseline value)

Table 8. Number of subjects with mucus in the stools at baseline and after 7 days of treatment

Product	n	baseline	7th day
Emospid®	40	12	3*
MMDH	20	7	3°

* p<0.01; ° p<0.05 (versus baseline value)

Table 9. Number of subjects with defecation disorders at baseline and after 7 days of treatment

Product	n	baseline	7th day
Emospid®	40	35	12*
MMDH	20	17	8°

* p<0.01; ° p<0.05 (versus baseline value)

In the Emospid® group, defecation urgency was found in 2 out of 14 pts. and need to defecate in 2 times was found in 1 out of 17pts.; the same parameters in the MMDH group correspond to 2 out of 7 and 1 out of 8 pts. (Table 10). At last (Table 11), acute events (external and/or internal oedema, external and/or internal thrombosis), that at baseline were found in 36 out 40 patients of the Emospid® group, were observed after 7 days of treatment in 10 out of 40 patients. In the MDHH group same acute events, observed at baseline in 19 out of 20 patients, were demonstrated after 7 days in 17 out of 20 pts. Taken

Table 10. Number of subjects with defecation urgency (DU) or with the need to defecate in 2 times (D2) at baseline and after 7 days of treatment

Product	DU baseline	DU 7th day	D2 baseline	D2 7th day
Emospid®	14/40	2/40*	17/40	1/40*
MMDH	7/20	2/20°	8/20	1/20°

* p<0.01; ° p<0.05 (versus baseline value)

Table 11. Number of subjects with acute events (external oedema=EE; internal oedema=IE; external thrombosis=ET; internal thrombosis=IT) or not (NE) at baseline and after 7 days of treatment

Product	n	baseline acute events					acute events at 7th day				
		EE	IE	ET	IT	NE	EE	IE	ET	IT	NE
Emospid®	40	16	22	2	2	4	4°	5*	0	0	30*
MMDH	20	8	12	1	2	1	3	3°	1	1	3

* p<0.01; ° p<0.05 (versus baseline value)

globally these results show a better efficacy for Emospid® if compared with the MMDH treatment.

Apart from parameters like bleeding intensity and pain severity score where the 2 treatments obtained comparable results, almost all the others parameters have shown differences in terms of the obtained results, with a global evaluation inferior, for the MMDH treatment by about 25-50%, according to the considered parameter, if compared with the Emospid® one.

From a clinical point of view, nevertheless the acute haemorrhoidal crisis corresponds to a painful situation where very often patients need analgesic treatment and/or incision followed by drainage of haemorrhoidal trombophlebitis, none out of 40 of the patients treated with Emospid® needed any pharmacological control of pain or a surgical approach. On the contrary 2 out of 20 of the patients treated with MMDH needed analgesics treatment requested at day 2 and 3.

Unwanted effects (1 in both groups) of gastric compliance lasted a few hours. No drop out anyway was observed. Compliance was lower for MMDH treatment due to the higher number of tablets to be taken daily (6 versus 3).

At last, the effect of treatments was not significantly different between the 2 groups with respect to blood pressure and biochemical variables (data not shown).

Conclusions

Since many elements from habits promote the development of the haemorrhoidal disease even in the same patient, lifestyle have to be corrected. A fiber-poor diet, promoting constipation, favours haemorrhoids. Foods like alcohol, spices, cocoa have to be avoided as well. As said before, constipation promotes haemorrhoids. Moreover, but with less incidence, diarrhea can promote haemorroids by irritating rectal mucosa and, consequently, by causing weakness of the anal veins walls. Heavy works or bad job positioning (i.e. driving) favours venous stasis and then haemorrhoidal disease.

Anyway, simply correcting this negative "styles" a patient may only reduce the risk of haemorrhoidal pathology. Besides that a pharmacological approach is needed. Along with anti-inflammatory and analgesic drugs, substances able to enforce mainly venous walls are described to counteract haemorrhoidal pathology preventing the risk of recurrency. Among these substances, especially bioflavonoids have got the attention of the medical practitioners (9).

Nevertheless bioflavonoids are commonly believed to be effective in counteracting chronic haemorrhoidal disease and/or in presence of a situation of chronic venous insufficiency, poorer, or less abundant, data are available concerning acute haemorrhoidal crisis. New pharmacological tools effective in avoiding or

delaying the need of an invasive, surgical, approach are then still needed.

Recently developed, Emospid®, is a 3-layered tablet containing separately 100 mg of Leucoselect Phytosome®, 30 mg of CAST, and 80 mg of Mirtoselect®. Being these 3 active ingredients also used in 3 different pharmaceutical specialities (Endothelon®, Centellase®, Tegens®, respectively traded by Sanofi; Bayer and Sanofi again) used for haemorrhoidal disease and chronic venous insufficiency, we have assumed that the product, also due to the innovative galenical approach used to develop the formulation (Phytosome® and sustained releasing technologies), could determine appreciable clinical results in acute haemorrhoidal crisis, as well.

Being the micronized mixture of diosmin and hesperidin (MMDH) tablets (500 mg/tablet of diosmin and hesperidin in a ratio of 90:10) the best clinically described as effective in counteracting acute haemorrhoidal crisis, we have tested these 2 products in order to describe, comparing them, their clinical effectiveness.

As clearly shown in the Results section, Emospid® is able to determine a better clinical effectiveness in terms of reducing bleeding, pain, itching, tenesm, anal tone, defecation disorders, presence of mucus. It gives rise to less acute events like external and internal oedema, internal and external thrombosis. Finally, the treatment with Emospid® determines a better shift to a lower haemorrhoidal grade.

Such effectiveness is probably due the high rate of bioavailability of the single actives. They have been in fact formulated (by complexation in phytosome form or by modifying the releases in a time-dependant manner) with the aim to increase the oral bioavailability. As described in the Introduction section, this is very often the real limit of the bioflavonoids efficacy. The same poor oral bioavailability probably limits even the efficacy of MMDH and obliges to the use of very high dosage to get evident results (2000-3000 mg/day).

In conclusion, Emospid® seems to be effective for acute haemorrhoidal crisis. Its efficacy seems to be higher that the one shown by the most described bioflavonoids product available for the medical practitioner (MMDH). Its tolerability is very high. Compliance is acceptable, especially in comparison with the MMDH treatment. It is then to be considered a valid alternative to the usual oral treatments available as a first line product to limit acute haemorrhoidal crisis. In order to better confirm this possibility, a next step will be soon planned with the enrolling of a higher number of patients for testing the product, again in the acute haemorrhoidal crisis and in the chronic venous insufficiency (lower limbs). In this last clinical trial, the testing will be again against the MMDH product, being this last a very well known product described to be effective in counteracting most of the venous disorder.

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