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ORIGINAL ARTICLE

A pilot study on the efficacy and safety of preoperative micronized purified flavonoid fraction treatment and sucralfate-based rectal ointment on patients with grade II to IV hemorrhoidal disease

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ABSTRACT

BACKGROUND: Hemorrhoidal disease (HD) is a chronic and extremely common condition that negatively impacts patients' quality of life. The aim of the present study was to evaluate the changes in symptom severity and the need for further interventions following treatment with the oral micronized purified flavonoid fraction (MPFF) and a topical rectal ointment containing 3% sucralfate and herbal extracts (calendula, witch hazel leaf, chamomile).

METHODS: A consecutive series of patients aged 18 to 75 with symptomatic II to IV-degree HD classified according to the Goligher classification were prospectively enrolled between September and December 2023. All patients were proposed a hypothetical surgical strategy at time 0 (T0) based on clinical presentation. At T1 (60 days), 7 days before any subsequent procedure, a different colorectal surgeon from the one who conducted the initial assessment performed a reassessment. All enrolled patients underwent medical therapy with a 500 mg MPFF twice daily and rectal ointment twice daily for a duration of 60 days, in addition to conservative therapy. The primary outcome was the change in symptom severity from T0 to T1, assessed using the Hemorrhoidal Disease Symptom Score (HDSS), Short Health Scale HD (SHS-HD) and Vaizey incontinence score. Secondary outcomes included the rate of downgrading intervention.

RESULTS: The present study included 34 patients (15 [44.1%] female) with a median age of 46.5 years (IQR 30-66). Both HDSS and SHS statistically improved from a median value of 11 and 16 at T0 to 2 and 1 at T1, respectively (P<0.00001). In 12 out of 34 (35.3%) of patients, the second colorectal surgeon considered a less invasive treatment due to the downstaging of symptoms.

CONCLUSIONS: Combined local and systemic treatment with MPFF and sucralfate-based rectal ointment for HD patients showed clinical advantages both in terms of reducing the severity of the disease and allowing a less invasive treatment in certain cases.

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KEY WORDS: Hemorrhoids; Quality of life; Flavonoids.

Hemorrhoidal disease (HD) is a chronic and extremely common condition that significantly impacts quality of life (QoL). It is estimated that nearly half of the general population experiences at least one episode of acute distress from HD in their lifetime.[1] Over the past decades, significant advancements have been made in managing this condition, encompassing diagnostics, classification, and more conservative and long-term effective treatment techniques.[2]

Traditionally, the Goligher classification has been used to gauge the severity of the disease.[3, 4] However, several studies have shown that this classification does not adequately capture the patient's condition. It primarily evaluates the presence and severity of prolapse across four grades, with limited consideration for bleeding in Grade I HD and other symptoms, such as the degree of inflammation.

Over time, various conservative treatments with topically applied medications, such as rectal ointments, or systemic therapies have been introduced for very low to moderate degrees of prolapse (Goligher grades I-II). Initially valued for their effectiveness in early and less severe cases or for patients unfit for surgery, these treatments are now showing promising results in downstaging the disease before surgery and sometimes as standalone treatments for HD.[5-7]

Additionally, oral phlebotonics have proven effective in alleviating symptoms such as bleeding, itching, and pain, and in preventing the recurrence of HD.[6] These treatments include a variety of medications derived from natural sources like flavonoids or synthetic compounds such as calcium dobesilate.[7]

In this study, we examined two such products available on the market: a rectal ointment containing 3% sucralfate and herbal extracts (calendula, witch hazel leaf, chamomile), marketed as Emoflon™, and oral Micronized Purified Flavonoid Fraction (MPFF), a mix of 90% diosmin and 10% other flavonoids expressed as hesperidin (including hesperidin, diosmetin, linarin, isorhoifolin"), known as Daflon®.[8-10] The rectal ointment is intended to create a barrier, reduce irritative stimuli, lessen trauma from stool passage, and decrease microbial exposure to the anorectal area.[11, 12]

The aim of the present study was to evaluate the changes in symptom severity and the need for further interventions following treatment with MPFF and a topical rectal ointment at 60 days from the first patient's assessment.

Materials and methods

Study design

A consecutive series of patients with symptomatic II to IV-degree HD classified according to the Goligher classification were prospectively enrolled between September and December 2023. The present monocentric study was reported in accordance with the STROBE checklist.[13]

Procedural overview

All patients were proposed a hypothetical surgical strategy at time 0 (T0) based on clinical presentation. Subsequently, all enrolled patients underwent medical therapy with MPFF and rectal ointment for a duration of 60 days, in addition to conservative therapy (stool softeners and painkillers), at the end of which they underwent clinical re-evaluation for possible modification of the proposed treatment course.

The therapy was administered as follows:

• rectal ointment twice daily: patients received the rectal ointment containing 3% sucralfate and herbal extracts (Emoflon™, manufactured by Egis Pharmaceuticals PLC). This medication is available in Italy from 2019 and is intended for the treatment HD' symptoms and postoperative complications. Sucralfate is a basic aluminum salt of sucrose octasulfate with cytoprotective, antibacterial, and angiogenic properties. It promotes wound healing by both creating a mechanical barrier on the anal canal epithelium and binding the fibroblast growth factors;

• MPFF: patients were administered a 500 mg MPFF twice daily. MPFF consists of 90% micronized diosmin and 10% other flavonoids (hesperidin, diosmetin, linarin and isorhoifolin). This compound improves venous tone and lymphatic drainage reducing capillary hyperpermeability and protecting the microcirculation from inflammatory processes. Indeed, MPFF has the ability to inhibit leukocyte-endothelium interaction, thus preventing the activation of the inflammatory cascade involving cytokines, prostaglandins, leukotrienes, histamine, and other inflammatory mediators. Diosmin's absorption is enhanced by micronization to particles less than 2 microns.

Initial assessment (T0) and follow-up (T1)

Therefore, the study began with an initial patient assessment at T0, followed by a follow-up visit at T1, which occurred 60 days after conservative treatment and 7 days before any subsequent procedure. During the T0 visit, a range of treatment options, from conservative methods to surgical interventions (such as sclerotherapy, hemorrhoidal artery ligation-recto anal repair (HAL-RAR), or excisional hemorrhoidectomy), were discussed with the patient. These discussions were based on the patient's symptoms, prior consultations, and current clinical guidelines.

Reassessment at T1

At T1, a different colorectal surgeon from the one who conducted the initial assessment, and not aware of the clinical scenario, performed a reassessment. This reassessment aimed to determine if the originally planned procedure remained appropriate or needed adjustment. The reassessment considered whether the patient's condition had improved, making them eligible for less invasive

treatments, or whether they required more intensive interventions. Decisions were made based on the patient's response and preferences.

Data collection and analysis

Demographic data, symptom severity, quality of life, and continence levels were collected prospectively. The scale and type of painkiller use were documented at T0. Pain levels were measured using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain). Painkiller use was categorized by amount (0 = no painkillers; 1 = 1–3 per day for up to 2 days; 2 = 1–3 per day for more than 2 days; 3 = more than 3 per day for more than 2 days) and type (no painkillers, minor analgesics like 1 g paracetamol, or major analgesics like 600 mg ibuprofen or paracetamol 1000 mg with codeine 60 mg).

Eligibility criteria

Patients aged 18 to 75 with symptomatic II to IV-degree HD were considered eligible. Exclusions included those with cardiac disease, coagulopathy, colorectal or anal neoplasia, inflammatory bowel disease, other proctological diseases, recent anal procedures, pregnancy or breastfeeding, viral infections, proctitis, allergy to polidocanol, pelvic radiotherapy, or inability to follow-up postoperatively.

Procedure

At T0 all patients had a proctological examination, including digital rectal examination and anoscopy, to confirm HD severity and exclude other anorectal diseases. Treatment plans (sclerotherapy, HAL-RAR, or excisional hemorrhoidectomy) were adjusted at T1 based on the response to initial therapy.

Outcomes

The primary outcome was the change in symptom severity from T0 to T1, assessed using the Hemorrhoidal Disease Symptom Score (HDSS), Short Health Scale HD (SHS-HD),[14] and Vaizey incontinence score.[15] Secondary outcomes included the rate of intervention downgrading from more invasive procedures at T0 to less invasive or no intervention at T1.

Statistical analysis

All data were expressed as mean and standard deviation or median (interquartile range; IQR), otherwise specified. Normality was assessed by inspection of frequency histograms and with Kolmogorov-Smirnov Score.

Comparison of variables was performed with the Chi-square Test and the Student's *t*-test for categorical and continuous variables, respectively. Non-parametric analysis was performed with Mann-Whitney U Test. All statistical tests were two-sided, with a P value <0.05 considered as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (Ver. 26.0; IBM Corporation, Armonk, NY, USA).

Results

The present monocentric study included 34 patients (15 [44%] female) with a median age of 46.5 years (IQR 30-66). Most of them suffered from III-degree HD (58.8%) followed by II degree (23.5%) and IV degree (17.6%).

Data about the painkillers need are reported in Table I.

From T0 and T1 a statistically significant improvement was registered in the HDSS score showing a median value of 11 pre-treatment decreasing to 2 after 60 days (P<0.00001). Also, SHS demonstrated a notable improvement from a median value of 16 to 1 after conservative treatment with statistical significance (P<0.00001). On the contrary, Vaizey score showed no significant differences from T0 to T1 (P=0.5) as reported in Table II.

TABLE I.—*Patients' characteristics.*

Characteristics	Value
Gender	
Female	15 (44%)
Male	19 (56%)
Age, years (median, IQR)	46.5 (66-30)
Goligher grade	
II	8 (23.5%)
III	20 (58.8%)
IV	6 (17.6%)
Type of analgesia	
None	15 (44.1%)
Minor	10 (29.4%)
Major	9 (26.5%)
Frequency of analgesia	
None	15 (44.1%)
1-3 daily for ≤2 days	10 (29.4%)
1-3 daily for >2 days	9 (26.5%)

IQR: interquartile range

TABLE II.—*Differences in symptom scores from T0 to T1.*

Score	Timeline		P value
	T0	T1	
HDSS (median, IQR)	11 (12–9)	2 (3.25-0)	<0.00001
SHS (median, IQR)	16 (19.25 - 14)	1 (6-0)	<0.00001
Vaizey score (median, IQR)	0 (1-0)	0 (1-0)	0.5

IQR: interquartile range; HDSS: Hemorrhoidal Disease Symptom Score; SHS: Short Health Scale.

TABLE III.—*Distribution of treatments (planned and actual).*

Planned treatment	Actual treatment	Result N. (%)	Change
Sclerotherapy	Sclerotherapy	5 (14.7)	No change
HAL-RAR	HAL-RAR	7 (20.6)	N.=19 (55.9%)
Hemorrhoidectomy	Hemorrhoidectomy	7 (20.6)	
Sclerotherapy	No treatment	1 (2.9)	Downgrading
HAL-RAR	Sclerotherapy	7 (20.6)	N.=12 (35.3%)
Hemorrhoidectomy	HAL-RAR	4 (11.8)	
Hemorrhoidectomy	Sclerotherapy	0	
Sclerotherapy	HAL-RAR	1 (2.9)	Upgrading
Sclerotherapy	Hemorrhoidectomy	1 (2.9)	N.=4 (11.8%)
HAL-RAR	Hemorrhoidectomy	2 (5.9)	

HAL-RAR: hemorrhoidal artery ligation-recto anal repair.

In 19 (55.9%) patients, the second independent surgeon decided to maintain the same indication for surgical treatment as at time T0, while in 12 patients out of 34 (35.3%) a less invasive treatment was considered due to the downstaging of symptoms. Conversely, in four cases (11.8%), a more invasive treatment was recommended due to the worsening of the pathology (Table III).

Discussion

The present monocentric study highlights the effectiveness of preoperative treatment for HD, demonstrating that a combination of a rectal ointment and MPFF significantly reduced scores in the population enrolled in the study. This approach led to a general downstaging of HD and the selection of less invasive treatments (35.3%), a confirmation of the first therapeutic indication (55.9%), or an upgrade in the treatment in the minority of the cases (11.8%).

Indeed, the effectiveness of oral flavonoids in treating HD across all stages has been well-documented. The role of conservative therapy in the assessment of HD is now essential not only to treat those patients who are unfit for surgery but also to alleviate the symptoms, which sometimes have a serious impact on the patient's QoL. Moreover, also in the period before a more aggressive solution such as a surgical approach, they might have a role as bridge to surgery in terms of symptom relief and downstaging of the disease. In fact, it also offers an alternative option for patients who are temporarily unfit for surgery and is most often an effective attempt at a purely conservative resolution.

Alonso-Coello *et al.* were among the first to report the benefits of flavonoids on acute HD symptoms.[6] While the optimal dosages and durations of pre- and postoperative medications remain uncertain, they suggested that high-dose MPFF (3000 mg per day for the first 4 days and 2000 mg per day for 3 days) is most effective in the acute phase, with dosage reductions during the relief phase (1000 mg per day for 2 months) based on symptoms.[6] Fu *et al.*[16] supported the effectiveness of high doses (1800-2700 mg per day) in significantly reducing edema and pain, while lower doses (less than 1800 mg per day) improved clinical efficacy post-excision.

In our study, a constant dosage of 1000 mg per day was maintained, supplemented with topical ointment to enhance therapeutic effects. To date, limited research has explored combined local and systemic therapies for HD. Amaturo *et al.*[12] reported significant symptom reduction and high patient satisfaction with a combination of oral MPFF and topical sucralfate-based rectal ointment. Similarly, Gupta *et al.*[17] demonstrated the effectiveness of sucralfate cream over placebo in patients undergoing excisional hemorrhoidectomy due to higher bioavailability and minimal systemic side effects. Of exceptional importance is communication with the patient and discussion of the benefits and risks of all kinds of therapies. In addition, the patient must be made aware of changes in lifestyle, of symptoms that should be alarming for a worsening of the disease or that may exist but are mitigated; patients must also be made aware of the impact that this disease has or may have on their quality of life beyond the degree of severity according to Goligher. It is indeed necessary to explain in detail to the patient the complex mechanism of fecal continence and in particular the role of the hemorrhoid plexus in maintaining resting pressure and the consequent need for a step-up approach. Being such a common disease and having such a high impact on quality of life, the general trend and current scientific focus is on alternatives to the most common surgical approaches.[18] For this reason, there are numerous studies that have re-evaluated the possibility of treating moderate-grade disease, *e.g.* I to III-degree HD, with injection sclerotherapy with promising results.[19-21] Therefore, the advent of new systemic or topical pharmacological therapies such as rectal ointments that can work as standalone therapy or downstaging even severe disease and thus allowing treatment with minimally invasive surgical therapies represents a great opportunity for the patient to be assessed with precision medicine and tailored surgery.[22] However, excisional hemorrhoidectomy still remains the gold standard for the treatment of III and IV degree HD and large proportion of patients still has to undergo invasive therapy, often facing severe post-operative sequelae.[23, 24]

Moreover, the combination of oral MPFF and topical sucralfate-based rectal ointment could also play a key role in

the postoperative management of the HD patient.[16] Indeed, a recent meta-analysis of 22 Randomized Control Trials (RCTs) involving 2335 patients showed that MPFFs effectively reduced postoperative hemorrhoid complications, including bleeding, pain, and edema, enhancing the clinical efficacy of hemorrhoidectomy without adverse reactions.[16] Medkova *et al.*[25] also found that MPFFs lowered the incidence of thrombosis or edema and had higher patient-assessed treatment effects compared to the control group.

Limitations of the study

Despite its contributions, this study has limitations, including its non-randomized design, lacking control group, and small sample size. Guidelines support the conservative approach.[7, 26] However, variations in treatment options within the same classification grade (*e.g.*, Goligher II) reflect differing patient preferences and recovery expectations. Efforts were made to reduce selection bias through independent patient reassessment. The study's strengths include using validated scores for HD symptoms and quality of life impacts, with two independent investigators involved. The data appear to provide support for a strategy of intensifying or optimizing conservative therapy – using a combination of topical and systemic pharmacological therapies – in appropriately selected patients with hemorrhoids during a period of surveillance prior to a planned intervention. The novel approach of preoperative patient assessment and strategy alteration could reduce healthcare costs and improve HD management.

Conclusions

Combined local and systemic treatment with MPFF and sucralfate-based rectal ointment for HD patients showed several clinical advantages. This approach not only reduces the severity of the disease but also enables less invasive treatment options in certain cases. However, further prospective randomized clinical trials are essential to confirm these findings.

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Conflicts of interest
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