

# Management of hemorrhoidal disease: new generation of oral and topical treatments

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**Abstract.** – Hemorrhoidal disease is a widespread proctologic clinical entity. Even if surgical excision is an effective treatment, it only represents the standard procedure for patients with high-grade hemorrhoids. Considering that most cases are grade I or II hemorrhoids, oral or topical therapies are widely used despite, currently, there are no satisfactory options for these kinds of treatments. The pathology involves the degeneration of the supporting tissue of the anal cushions, causing venous dilation, blood stagnation, formation of edematous venous plexus covered by mucosa and inflammation. An effective treatment must, therefore, be multi-targeted and capable of acting on all the pathological mechanisms simultaneously. During the 8th National Congress of the Italian Association of Colorectal Surgery (SICCR), some clinical evidence of hemorrhoidal disease has been discussed along with new opportunities in oral and topical treatment options.

Among these, the effectiveness and the safety of two innovative products, a sublingual nanoemulsion and a liquid bandage, has been reported.

*Key Words:*

Hemorrhoidal disease, Oral treatments, Topical treatments, Liquid bandage.

## Introduction

Hemorrhoidal disease is a very common proctologic clinical entity, especially in patients who are >50 years. Even if it is difficult to establish its real impact since only a minority of the patients consults a doctor, it is estimated that hemorrhoidal disease affects nearly 4% of the world's population, causing considerable discomfort and worsening the patient's quality of life<sup>1</sup>. In Italy, the prevalence of hemorrhoidal disease is approximately 1,000,000 new cases per year (2% of Italy's population)<sup>2</sup>.

In the 8<sup>th</sup> National Congress of the Italian Association of Colorectal Surgery (SICCR), which was held in Biella (Italy) on 12 November 2019, Italian experts met to discuss the clinical evidence of hemorrhoidal disease during a symposium on practical aspects about the management of this common disease, focusing on recent improvements in oral and topical treatment options.

### *Hemorrhoidal Disease*

Hemorrhoids are normal structures of the human body, distinguished internally and externally by an anatomical boundary called dentate line<sup>3</sup>. The normal internal hemorrhoidal plexus consists of three so-called vascular cushions, or piles, located at the left lateral (3 O'clock), right anterior (11 O'clock) and right posterior (7 O'clock) sectors of the anus<sup>4</sup>, and at least three others elsewhere (at 1, 5 and 9 O'clock)<sup>5</sup>, whose positions correspond to the location of the main terminal arterial branches in the submucosa. They are constituted by large arteriovenous shunt, supported by elastic tissue.

Hemorrhoidal disease is the result of an abnormal enlargement of anal cushions due to different etiologic factors. Although genetic factors contribute to developing hemorrhoids, other predisposing factors have been claimed. They include obesity, prolonged straining and prolonged standing position. Many dietary factors, including a low-fiber diet, spicy foods and alcohol intake, have been implicated, but reported data are inconsistent<sup>6</sup>.

Approximately four out of ten patients with hemorrhoids are symptomatic<sup>7</sup>. Bleeding is the most common symptom and is usually the first complaint of the patient, followed by local swelling and anal prolapse. Mucous discharge and consequent soiling and itching are both markers of

advanced disease. A feeling of incomplete evacuation or rectal fullness is also reported<sup>8</sup>. Pain is not a typical symptom, unless in the case of complications, such as edema, thrombosis, ischemia and strangulation.

The diagnosis of hemorrhoids relies mainly on a thorough history and physical examination of the patient, obtained by perineal inspection, a digital rectal examination, followed by anoscopy<sup>9</sup>. However, colonoscopy is mandatory to rule out colon neoplasia particularly in high-risk patients<sup>10</sup>. Differential diagnosis with other anal diseases includes anal fissure, abscess, carcinoma, and pudendal neuropathy, particularly in the presence of anal pain, which is commonly reported in the mentioned conditions and infrequent in hemorrhoidal disease, apart from complicated ones.

The severity of hemorrhoidal disease is graded into four stages according to Goligher's classification, based on the degree of prolapse through the anus and its tendency to reduce spontaneously or manually<sup>11</sup>. The vast majority of patients (>90%) present grade I or II, where medical management and lifestyle interventions, such as increasing fiber and fluid intake, avoiding prolonged standing position and physical activity, are successfully employed<sup>12</sup> and can help to prevent hemorrhoidal disease.

In case of unresponsive disease, ambulatory treatments are available and report up to 90% of success. Rubber banding<sup>13</sup> and, more recently, sclerosing injections<sup>14</sup> have shown to be very effective. However, surgical treatment can be effective in case of more advanced disease<sup>13,15</sup>.

SICCR has recently been published a consensus statement, with the aim to provide evidence-based data, allowing a personalized and appropriate management of hemorrhoid treatment<sup>16</sup>. In addition, it informs patients about the possibility for the management of their condition<sup>16</sup>.

A particular condition is represented by the occurrence of hemorrhoidal disease during pregnancy, where its etiology has been related to specific factors, such as hormones, increased circulating blood volume, increased pelvic pressure, and pelvic vascular engorgement<sup>17</sup>. Although these factors are different from those reported in the general population, treatment of hemorrhoidal disease in pregnancy continues to rely upon generic and empiric suggestions, such as increased fiber and fluid intake<sup>18</sup>. This area warrants further investigation in order to identify a targeted etiological treatment.

### ***Management of Hemorrhoidal Disease: Improvement of Oral and Topical Treatments***

Even if surgical excision is an effective treatment, it only represents the standard procedure for high-grade hemorrhoids.

The main therapeutic options for low-grade hemorrhoids can be divided into office-based procedures and medical treatment.

Office-based procedures are rubber band ligation, injection sclerotherapy, infrared/radiofrequency coagulation and cryotherapy<sup>19,20</sup>.

Medical treatments comprise modern drugs and traditional medicine, available in a variety of formulations, including pill, suppository, cream, and wipes. Flavonoids, in a purified preparation or as part of the derivative of the Ginkgo tree, are widely used for relief of acute symptoms. They are able to increase vascular tone, reduce venous capacity, decrease capillary permeability, and facilitate lymphatic drainage, as well as having anti-inflammatory effects<sup>21</sup>. Calcium dobesilate, nitrates and nifedipine are also effective and well tolerated as treatment of hemorrhoids.

Characteristics of principal hemorrhoids treatment options are summarized in Table I.

Oral and topical administrations are the most used for the treatment of low-grade hemorrhoids<sup>12</sup> but unfortunately, these kinds of treatment administrations present criticism.

Some physiological mechanisms can reduce intestinal absorption of the active ingredients of the drugs taken orally. Specifically, the absorption by the mucous secretions and the cytochrome CYP3A and P450 activity, or the extrusive activity of the P glycoprotein, can make the active ingredient unavailable. The peptide nature of the compounds can cause their gastric hydrolysis. Finally, a reduced inflow through enteric tight junctions or their biotransformation by the saprophytic flora are concurrent factors causing a reduced intestinal absorption of the active ingredients<sup>22</sup>.

Consequently, only a small percentage of active compounds is actually absorbed, requiring high doses of treatment to reach the therapeutic level.

Considering that a reduction of particle size has a great impact on the extent of absorption, as observed with the flavonoid diosmin, which demonstrated to have a better clinical efficacy with a micronized formulation<sup>23,24</sup>, a sublingual nanoemulsion formulation has been patented and proposed for the administration of different active ingredients, to counteract the main symptoms of hemorrhoids.

**Table I.** Hemorrhoids therapeutic options.

	Therapeutic effect/advantages	Adverse events/limitations
<b>Office-based procedures</b>		
Rubber band ligation	Cut-off of the blood flow to the hemorrhoid. Safe, lowest incidence of recurrent symptom and need for retreatment <sup>27</sup>	Pain, bleeding. Contraindicated in patient with anticoagulants or bleeding disorder, and those with concurrent anorectal sepsis <sup>27</sup>
Injection sclerotherapy	Scarring and subsequent fixation of mucosa to the submucosa	Low occurrence of pain and bleeding <sup>28</sup>
Photocoagulation	Necrotization of the tissue. Associated with less pain because there is no mucopexy during the procedure	High failure rate <sup>27</sup>
Cryotherapy	Creation of submucosal fibrosis to correct prolapse and bleeding	Postoperative swelling and lower digestive tract hemorrhage <sup>29</sup>
<b>Medical treatments</b>		
Flavonoids	Beneficial effects on bleeding, pruritus, discharge and overall symptom improvement	Autonomic and mild gastrointestinal symptoms <sup>30</sup>
Calcium dobesilate	Vascular protection and veno-tonic action	Fever, arthralgias and gastrointestinal effects <sup>31</sup>
Nitrates	Inhibitory neurotransmitter in the internal sphincterchemical. Can provide sphincterotomy without the risk of permanent incontinence	Can cause headaches <sup>32</sup>
Nifedipine	Effective for pain relief	No commercially available preparation <sup>33</sup>

Emortrofine® Oro<sup>1\*</sup> (*Boswellia* dry extract, diosmin, hesperidin, lysine, cysteine, ruscus dry extract, vitamin E, copper and arginine) represents the first sublingual nanoemulsion, which allows a multiple target activity and the maximum bio-availability of its components in a short time.

Moreover, the nanoemulsion in contact with saliva creates micellar systems, which encapsulate the lipophilic components and make possible the quick and complete absorption of the active ingredients at a sublingual level. Compared to the traditional tablet administration, this kind of formulation allows a lower dosage of its components because it guarantees a more effective sublingual absorption. This aspect is particularly important with regard to the flavonoid component, for which it is necessary to check the daily dosage.

Emortrofine® Oro also favors a better treatment compliance, because it involves the administration of three daily doses (reduced to one, after 6 days of treatment) instead of multiple daily tablets.

In a recent observational study, Emortrofine® Oro demonstrated to be safe and effective as pre-operative treatment in a group of advanced hemorrhoid patients. The study demonstrates a significant efficacy in mitigating reported symptoms (bleeding, prolapse, itching, pain) and on local inflammation signs (dystrophy de-epithelization, edema), allowing the patient to deal with surgery in better conditions (Orefice et al, data not shown).

Topical treatments may be effective in selected groups of hemorrhoidal patients, in particular in patients with high resting anal canal pressures. The primary objective of most topical treatment aims to control the symptoms rather than to cure it. These topical medications can contain various ingredients, such as local anesthesia, corticosteroids, antibiotics and anti-inflammatory drugs<sup>25</sup>.

Main concerns of topical treatments regard their prolonged application (>15 days) that can induce sensitization reactions, immunosuppression and vessel reactivity (due to cortisone)<sup>26</sup>, irritation and habituation (due to lidocaine).

An improvement of this kind of treatment is represented by Emortrofine® Gel<sup>\*</sup>, a patented hypertonic, viscous and osmotically active solution based on *Vitis vinifera*, cranberry, omega-3 and peppermint essential oil. Emortrofine® gel is the first transparent liquid bandage with the charac-

\*The use of commercial name of the product is for descriptive purposes only and does not imply endorsement.

teristics of the ideal topical treatment, as it stays *in situ* for prolonged time, has film-forming and protective activities and a multi-target action (anti-inflammatory, moisturizing, soothing and healing).

The clinical effectiveness of Emortrofine<sup>®</sup> gel has been tested in a multicenter, double-blind, randomized controlled clinical study in patients with grade I-III hemorrhoidal disease. The results show that Emortrofine<sup>®</sup> gel application generates a robust outflow of the hypotonic liquid accumulated inside the hemorrhoidal lesions. Liquid exudation reduces the lesion volume and favors its regression, which, in turn, alleviates the pressure, reducing pain and improving stool passing. Noteworthy, the benefits of treatment persist even 1 week after stopping treatment<sup>1</sup>.

Some clinical experiences suggest that Emortrofine<sup>®</sup> gel can be used to replace treatments containing mesalazine, which favors the development of sensitization reactions, even if more evidence is needed to confirm this indication.

The use of this device could be suggested also for the hemorrhoidal disease related to pregnancy and post-partum. Considering the lack of guidelines for the treatment of this category of patients, this represents an important novelty.

## Conclusions

Although surgery is an effective treatment of hemorrhoids, it is reserved for advanced disease and it can be associated with appreciable complications. Meanwhile, non-operative treatments are often not fully effective, in particular, those of a topical or oral approach. Hence, improvements in these kinds of treatments are needed.

Emortrofine<sup>®</sup> Oro and Emortrofine<sup>®</sup> gel are two innovative products based on patented technologies that ensure a multi-target action against the main symptoms of hemorrhoidal disease. Emortrofine<sup>®</sup> Oro is a sublingual nanoemulsion that allows a faster and complete absorption of all its components, compared to traditional tablet administration. Emortrofine<sup>®</sup> gel is the first transparent liquid bandage that demonstrates a clinical effectiveness in reducing the symptoms of hemorrhoidal disease. In addition, since Emortrofine<sup>®</sup> gel has no contraindications for use in pregnancy, further studies are guaranteed to obtain more data regarding its use in this category of patients, for which there is currently no specific treatment.

Overall, thanks to their formulation and composition, both treatments represent an improvement of traditional oral and topical treatments used for hemorrhoidal disease.

In conclusion, even if further clinical studies are needed to confirm to the clinical evidence collected so far, results suggest a therapeutic potential of this new generation of treatments, which should be exploited for other similar topical pathologies.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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## Disclosure

CR, GM, RP, RO have no conflicts of interest to declare. DT is a consultant Agave SRL, Italy.

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## References

- 1) GEORGES M, BEN ACHOUR HM, ADEL ADLY S, TROUILLER R, SHRIVASTAVA R. Clinical efficacy of a new generation of multi-target, anti-edematous, anti-inflammatory, tissue repairing topical polymeric liquid bandage for the treatment of internal hemorrhoids. *J Clin Exp Dermatol Res* 2017; 8: 4.
- 2) NASTRO P, BRACALE U, ROMANO G. Surgical treatment of haemorrhoidal disease: a survey of the regional area of Campania in Italy. *Ann Ital Chir* 2004; 75: 615–619.
- 3) SANDLER RS, PEERY AF. Rethinking what we know about hemorrhoids. *Clin. Gastroenterol. Hepatol* 2019; 17: 8-15.
- 4) MARGETIS N. Pathophysiology of internal hemorrhoids. *Ann F Gastroenterol* 2019; 32: 1-9.
- 5) RATTO C, PARELLO A, DONISI L, LITTA F, ZACCONE G, DOGLIETTO GB. Assessment of haemorrhoidal artery network using colour duplex imaging and clinical implications. *Br J Surg* 2012; 99: 112-118.
- 6) LODER PB, KAMM MA, NICHOLLS RJ, PHILLIPS RK. Haemorrhoids: pathology, pathophysiology and aetiology. *Br J Surg* 1994; 81: 946-954.



- 7) RISS S, WEISER FA, SCHWAMEIS K, RISS T, MITTLBÖCK M, STEINER G, STIFT A. The prevalence of hemorrhoids in adults. *Int J Colorectal Dis* 2012; 27: 215-220.
- 8) LOHSIRIWAT V. Hemorrhoids: from basic pathophysiology to clinical management. *World J Gastroenterol*. 2012; 18: 2009-2017.
- 9) CENGIZ TB, GORGUN E. Hemorrhoids: a range of treatments. *Cleve Clin J Med* 2019; 86: 612-620.
- 10) GUPTA PJ. Advanced grades of bleeding hemorrhoids in a young boy. *Eur Rev Med Pharmacol Sci* 2007; 11:129-132.
- 11) RUBBINI M, ASCANELLI S. Classification and guidelines of hemorrhoidal disease: Present and future. *World J Gastrointest Surg* 2019; 11: 117-121. <https://doi.org/10.4240/wjgs.v11.i3.117>
- 12) SANCHEZ C, CHINN BT. Hemorrhoids. *Clin Colon Rectal Surg* 2011; 24: 5-13.
- 13) TROMPETTO M, CLERICO G, COCORULLO GF, GIORDANO P, MARINO F, MARTELLUCCI J, MILITO G, MISTRANGELO M, RATTO C. Evaluation and management of hemorrhoids: Italian society of colorectal surgery (SICCR) consensus statement. *Tech Coloproctol* 2015; 19: 567-575.
- 14) LOBASCIO P, LAFORGIA R, NOVELLI E, PERRONE F, DI SALVO M, PEZZOLLA A, TROMPETTO M, GALLO, G. Short-term results of sclerotherapy with 3% polidocanol foam for symptomatic second- and third-degree hemorrhoidal disease. *J Invest Surg* 2020; 1-7. doi: 10.1080/08941939.2020.1745964. Online ahead of print.
- 15) DAVIS BR, LEE-KONG SA, MIGALY J, FEINGOLD DL, STEELE SR. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the management of hemorrhoids. *Dis. Colon Rectum* 2018; 61: 284-292.
- 16) GALLO G, MARTELLUCCI J, STURIALE A, CLERICO G, MILITO G, MARINO F, COCORULLO G, GIORDANO P, MISTRANGELO M, TROMPETTO M. Consensus statement of the Italian society of colorectal surgery (SICCR): management and treatment of hemorrhoidal disease. *Tech Coloproctol* 2020; 24: 145-164.
- 17) AVSAR AF, KESKIN HL. Haemorrhoids during pregnancy. *J Obstet Gynaecol* 2010; 30: 231-237.
- 18) WHO RECOMMENDATIONS ON ANTENATAL CARE FOR A POSITIVE PREGNANCY EXPERIENCE. WHO Guidelines Approved by the Guidelines Review Committee. World Health Organization, Geneva (2016).
- 19) LOHSIRIWAT V. Treatment of hemorrhoids: a coloproctologist's view. *World J Gastroenterol* 2015; 21: 9245-9252.
- 20) FILINGERI V, ANGELICO R, BELLINI MI, MANUELLI M, SFORZA D. Ambulatory therapy with combined hemorrhoidal radiocoagulation. *Eur Rev Med Pharmacol Sci* 2013; 17: 130-133.
- 21) STRUCKMANN JR, NICOLAIDES AN. Flavonoids. A review of the pharmacology and therapeutic efficacy of Daflon 500 mg in patients with chronic venous insufficiency and related disorders. *Angiology* 1994; 45: 419-428.
- 22) TAMAI I. [Molecular characterization of intestinal absorption of drugs by carrier-mediated transport mechanisms]. *Yakugaku Zasshi* 1997; 117: 415-434.
- 23) GARNER RC, GARNER JV, GREGORY S, WHATTAM M, CALAM A, LEONG D. Comparison of the absorption of micronized (Daflon 500 mg) and nonmicronized 14C-diosmin tablets after oral administration to healthy volunteers by accelerator mass spectrometry and liquid scintillation counting. *J Pharm Sci* 2002; 91: 32-40.
- 24) RUSSO R, CHANDRADHARA D, DE TOMMASI N. Comparative bioavailability of two diosmin formulations after oral administration to healthy volunteers. *Molecules* 2018; 23: 2174.
- 25) JOHANSON JF. Nonsurgical treatment of hemorrhoids. *J Gastrointest Surg* 2002; 6: 290-294.
- 26) BAECK M, MAROT L, NICOLAS J-F, PILETTE C, TENNSTEDT D, GOOSSENS A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. *Allergy* 2009; 64: 978-994.
- 27) MACRAE HM, McLEOD RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. *Dis Colon Rectum* 1995; 38: 687-694.
- 28) COCORULLO G, TUTINO R, FALCO N, LICARI L, ORLANDO G, FONTANA T, RASPANTI C, SALAMONE G, SCERRINO G, GALLO G, TROMPETTO M, GULOTTA G. The non-surgical management for hemorrhoidal disease. A systematic review. *G Chir* 2017; 38: 5-14.
- 29) MACLEOD JH. In defense of cryotherapy for hemorrhoids. A modified method. *Dis Colon Rectum* 1982; 25: 332-335.
- 30) MISRA MC, IMLITEMSU. Drug treatment of haemorrhoids. *Drugs* 2005; 65: 1481-1491.
- 31) ALLAIN H, RAMELET AA, POLARD E, BENTUÉ-FERRER D. Safety of calcium dobesilate in chronic venous disease, diabetic retinopathy and haemorrhoids. *Drug Saf* 2004; 27: 649-660.
- 32) LODER PB, KAMM MA, NICHOLLS RJ, PHILLIPS RK. 'Reversible chemical sphincterotomy' by local application of glyceryl trinitrate. *Br J Surg* 1994; 81: 1386-1389.
- 33) PERROTTI P, ANTROPOLI C, MOLINO D, DE STEFANO G, ANTROPOLI M. Conservative treatment of acute thrombosed external hemorrhoids with topical nifedipine. *Dis Colon Rectum* 2001; 44: 405-409.