Recent Advances in the Management of Hemorrhoid Disease

Reviewed by:
Dr. Jayanta Mukherjee
MD (Medicine), DM (Gastroenterology)
ILS Hospitals, Kolkata

Burden of Hemorrhoid Disease

Hemorrhoid disease is one of the most common anorectal disorders that affect people worldwide.[1,2] Hemorrhoids, with a reported prevalence of 4% up to 55% of general population, affect people across all ages, sex, races, and ethnicities.[1-3] Although the problem can occur at any age and can affect both men and women, the peak prevalence has been reported between 45 and 65 years of age, with a subsequent decrease after the age of 65 years.[4,5] Despite its prevalence and low morbidity, hemorrhoid disease is a significant health care burden with a high impact on quality of life.[1,5,6]

Guidelines from across the world unanimously recommend a conservative approach toward the management of the disease. The majority of patients are treated satisfactorily with medical management; hence, medical management plays an important role in the treatment of hemorrhoidal disease. Medical management has essentially two components — lifestyle/dietary changes and oral phlebotonic drugs. By incorporating these two modalities, the majority of patients can avoid surgery especially in the early stages of the disease.[1]

Classification and Grading

Hemorrhoids are usually categorized according to their origin relative to the dentate line and degree of prolapse.[6-9] A hemorrhoid classification system helps select from the different treatments, and also to compare them.[10] On the basis of position, hemorrhoids are classified as internal, external and mixed hemorrhoids. Internal hemorrhoids originate above the dentate line and are covered by anal mucosa, whereas external hemorrhoids originate below the dentate line and are covered with squamous epithelium. Mixed or interno-external hemorrhoids appear both above and below the dentate line.[7-9]

Table 1: Classification of internal hemorrhoids

Grade	Description
I (First degree hemorrhoids)	• Normal appearance • Bleeding but non-prolapsing hemorrhoids
II (Second degree hemorrhoids)	• Hemorrhoids prolapse on straining but reduce spontaneously
III (Third degree hemorrhoids)	• Hemorrhoids prolapse through the anus on straining or exertion • Require manual reduction
IV (Fourth degree hemorrhoids)	• Permanent prolapsing hemorrhoids • Non-reducible • Include acutely thrombosed, incarcerated internal hemorrhoids and incarcerated, thrombosed hemorrhoids involving circumferential rectal mucosal prolapse

Based on their appearance and degree of prolapse, internal hemorrhoids are further graded, according to the Goligher classification, as first-degree hemorrhoids (grade I), second-degree hemorrhoids (grade II), third-degree hemorrhoids (grade III), and fourth-degree hemorrhoids (grade IV); Table 1.[7,8,10] External hemorrhoids are susceptible to thrombosis, and may be classified as acute (hemorrhoidal thrombosis) or chronic (anal skin tags).[11,12]

Clinical Presentation of Hemorrhoids

Approximately 40% of individuals with hemorrhoids are asymptomatic. For symptomatic hemorrhoids, there is great variance in the constellation of symptoms.[6] The most common manifestation of hemorrhoids is painless rectal bleeding with or without defecation, a swelling,

Table 2: Clinical presentation of hemorrhoids

Internal hemorrhoids	External hemorrhoids
• Bleeding • Tissue prolapse and mucus discharge • Mild fecal incontinence • Sensation of perianal fullness • Irritation of perianal skin	• Pain (if thrombosed) • Burning sensation • Trouble in maintaining perianal hygiene • Itching

Box 1: Pathological changes associated with hemorrhoids

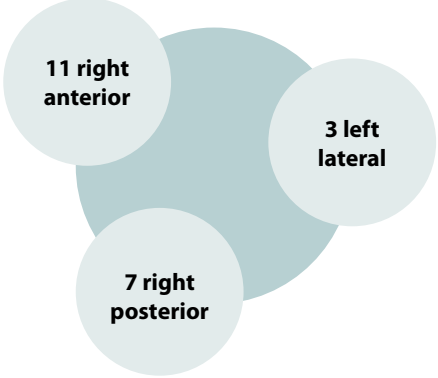
- Abnormal venous dilatation
- Vascular thrombosis
- Degenerative process in the collagen fibers and fibroelastic tissues
- Distortion and rupture of the anal subepithelial muscle
- Inflammation
- Mucosal ulceration
- Ischemia

mild discomfort or irritation. The blood is bright red and coats the stool at the end of defection. Other symptoms may include sensation of tissue prolapse, soilage or mucous discharge, pruritus ani, and hygiene problems. Patients with large hemorrhoids also report a feeling of incomplete evacuation or rectal fullness. External hemorrhoids are associated with pain and bleeding when thrombosis or ulceration occurs. On the other hand, internal hemorrhoids, otherwise painless, become symptomatic when they prolapse, thrombose, bleed or get strangulated (Table 2).[6,8,13]

Pathophysiology of Hemorrhoids

Hemorrhoids are normal anal cushions of submucosal vascular tissue surrounding the anastomoses between the superior rectal artery and the superior, middle, and inferior rectal veins.[6,14] There are three main anal cushions, located in the left lateral, the right posterolateral, and the right anterolateral aspect of the anal canal (3, 7, and 11 o'clock positions); Figure 1.[13,15,16] These vascular cushions

Figure 1: Common sites of major anal cushions



are clusters of elastic connective tissue and smooth muscle. Hemorrhoidal tissue is important in protecting the anal sphincter during defecation. Besides, the vascular cushions also contribute to anal continence because these provide 15%-20% of the resting anal pressure required to maintain continence.[12,13,15]

Importantly, hemorrhoids become a disease when pathologic and dilated changes occur in the vascular cushions and cause the development of symptomatic hemorrhoids.[12,15] The term 'hemorrhoid' is usually referred to the pathological condition of symptomatic hemorrhoid, which is associated with symptoms such as bleeding, prolapse, pain, pruritus, mucus discharge, and thrombosis.[6,14]

The pathophysiology of hemorrhoid development is multifaceted and includes several theories, such as sliding anal canal lining, hyperperfusion of hemorrhoid plexus, vascular abnormality, tissue inflammation and internal rectal prolapse. Among them, the theory of sliding anal canal lining is the most-widely accepted theory, which suggests that hemorrhoids develop when the supporting tissues of the anal cushions deteriorate or degenerate.[7,8,16] Various pathological changes are observed in the anal cushions of patients with hemorrhoids, which include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibers and fibroelastic tissues, distortion and rupture of the anal subepithelial muscle (Box 1). Therefore, hemorrhoids are the pathological term used to describe the abnormal downward displacement of the anal cushions resulting in venous dilatation.[8]

Risk Factors for Hemorrhoids

Several risk factors have been associated with hemorrhoid development including aging, obesity, depressive

mood and pregnancy. Besides, factors that increase intra-abdominal pressure, such as prolonged straining and constipation, are considered to contribute to the development of hemorrhoids due to compromised venous drainage of hemorrhoid plexus. Constipation and prolonged straining are thought to increase the shearing force on the anal cushions, further predisposing to the formation of hemorrhoids. Moreover, prolonged straining may lead to the development of symptoms such as bleeding and prolapse in patients with a history of hemorrhoidal disease.[7-9,17]

In addition, pregnancy predisposes women to congestion of the anal cushion and symptomatic hemorrhoids; however, they usually resolve soon after birth. Certain dietary factors and lifestyle, including low fiber diet, spicy foods and alcohol intake have also been associated with the development of hemorrhoids and may exacerbate acute hemorrhoid symptoms (Box 2).[7,8]

Clinical Evaluation

The definite diagnosis of hemorrhoidal disease relies on an accurate history and a careful clinical examination which should include a digital rectal examination and anoscopy in the left lateral position.[8] A complete evaluation of the colon is recommended in the following clinical scenarios:[9]

- Patients with iron deficiency anemia
- Positive fecal occult blood test
- Age ≥50 years with no complete colon evaluation within the past 10 years
- Age ≥40 years, with positive family history for a single first-degree relative with colorectal cancer or adenoma diagnosed at age ≤ 60 years and no complete examination within 10 years
- Age ≥40 years, with positive family history for more than one first-degree relative with adenoma or colorectal carcinoma diagnosed at age ≤60 years and no complete examination within the past 5 years.

Box 2: Risk factors for hemorrhoid development

- Aging
- Obesity
- Pregnancy
- Depression
- Prolonged straining
- Constipation
- Low fiber diet
- Spicy foods
- Alcohol consumption

Treatment Approach to Hemorrhoids

The management of hemorrhoids is guided by the degree and severity of symptoms, patient's age, and comorbidities, and it ranges from dietary and lifestyle modification to radical surgery.[7,8,13,18] One general principle is that the least-invasive approaches should be considered first given the physiologic importance of the hemorrhoid cushions.[6,13]

Conservative Management

Diet and lifestyle undoubtedly play an important role in hemorrhoid management.[5] Dietary modification consists of adequate fluid and fiber intake and counseling regarding defecation habits.[1] An increase in dietary fiber and oral fluids in the diet may help eliminate straining during defecation, thus reducing the damage caused by the shearing action of passing hard stool on the anal mucosa.[8] Clinical studies of hemorrhoids substantiate the beneficial effect of fiber in the treatment of symptomatic hemorrhoids for relieving overall symptoms such as bleeding, pain, prolapsing and itching.[9,19] In cases of hemorrhoids, fibre supplementation has been shown to relieve symptoms and minimize risk of bleeding by approximately 50%.[5]

In addition to increasing dietary fiber and oral fluids, other lifestyle modifications may play a role in the treatment or prevention of hemorrhoids. These changes include reducing fat consumption, having regular exercise, improving anal hygiene, avoiding straining and reading on the toilet, and avoiding medication that causes constipation or diarrhea.[8]

Nonsurgical Office-based Procedures

Early grade hemorrhoids that do not respond to conservative management can be managed with office procedures, such as rubber band ligation (RBL), sclerotherapy, infrared coagulation, and laser therapy. These procedures aim to decrease blood flow to the hemorrhoid, reduce the redundant tissue and fix the hemorrhoid to the underlying tissue to reduce prolapse.[2]

Rubber band ligation is the most commonly performed procedure in the office and is indicated for grade II and III internal hemorrhoids. RBL uses a device that allows a rubber band to be applied to each hemorrhoid via a proctoscope. This band constricts the blood supply causing the hemorrhoid to become ischemic before being sloughed approximately 1–2 weeks later. The resultant fibrosis reduces any element of hemorrhoidal prolapse that may have been present.[5,6]

Sclerotherapy is indicated for patients with grade I and II internal hemorrhoids and similar to RLB, sclerotherapy does not require local anesthesia. Performed through an anoscope, internal hemorrhoids are located and injected with a sclerosant material—usually a solution including phenol in vegetable oil—into the submucosa. The sclerosant subsequently causes fibrosis, fixation to the anal canal, and eventual obliteration of the redundant hemorrhoidal tissue.[6] Surgical consultation is needed in case of failure of conservative treatments including medical therapy.[2]

Pharmacological therapy

For pharmacological therapy, several treatment options, including both topical and oral medications are available. Nonetheless, there is a dearth of data to support the efficacy of topical formulations for symptomatic hemorrhoids. In this context, oral preparations, such as bioflavonoids, may seem a rational approach, and could in fact be considered the first-line agents for hemorrhoids treatment.[7,20] Flavonoids are the most common oral phlebotonic drugs used for treating hemorrhoids. Flavonoids have been found to exert positive effects in hemorrhoids patients through several possible mechanisms - by increasing venous tone, reducing venous capacity, decreasing capillary permeability, facilitating lymphatic drainage and by exerting an anti-inflammatory effect.[7,8,18] Arguably, the oral bioflavonoid diosmin has emerged as a highly potent agent in treatment of hemorrhoids since it possibly affects all pathophysiological aspects of hemorrhoids.[21,22]

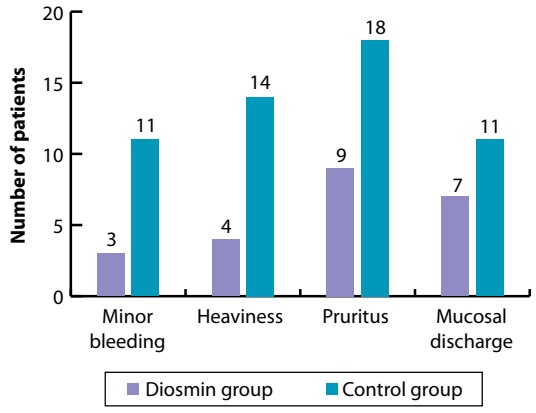
Diosmin: A Fitting Molecule for Conservative Approach

Diosmin, first introduced as a therapeutic agent in 1969, is a naturally occurring flavonoid glycoside, and is considered to be a vascular-protecting agent with multimodal action; justifying its role in treatment of hemorrhoids and chronic venous insufficiency. Diosmin has been widely used for more than 30 years worldwide as a phlebotonic and vascular protecting agent with good efficacy and safety profile. Moreover, being a flavonoid, diosmin also exhibits anti-inflammatory, free-radical scavenging, and anti-mutagenic properties.[22] Of note, diosmin exhibits excellent tolerability profile, which makes the drug very easy to handle by the general practitioner, and also useful to the proctologist in the preparation of the patient to further treatments.[20] Besides, diosmin may be used in conjunction with sclerotherapy, surgery and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible.[23]

The pharmacokinetic data has reported that the drug attains maximum plasma concentration after about one hour of administration, and demonstrates a half life of 26 to 43 hours.[24,25] Diosmin effectively targets the pathophysiology of hemorrhoids, and hence can reduce the associated disease symptoms including pain, edema, and heaviness. Also, it could affect the recurrence as well, and therefore appears to be well-suited to the conservative approach in hemorrhoids.[23]

A phase II randomized, prospective, observer-blinded, placebo-controlled clinical trial,[26] conducted among 86 consecutive patients with grades III and IV acute mixed hemorrhoids, demonstrated markedly greater improvement in pain, heaviness, bleeding, and pruritus from baseline to the 2nd and 8th week after surgery in patients on diosmin therapy compared with the controls (Figure 2). Moreover, those taking diosmin had a shorter length of hospital stay after surgery. The study suggested that diosmin is effective in ameliorating postoperative symptoms of hemorrhoids and must be considered in the initial treatment after hemorrhoid surgery.

Figure 2: Postoperative symptoms of diosmin versus control groups in the 2nd week of hemorrhoid surgery



Mechanism of Action of Diosmin

Diosmin exhibits a multifaceted mechanism of action, which includes improvement of venous tone, increased lymphatic drainage, protection of capillary bed microcirculation, inhibition of inflammatory reactions, and reduced capillary permeability. Diosmin exerts its phlebotonic effect by prolonging the vasoconstrictor effect of norepinephrine on vein wall, enhances venous tone, and thus reduces distensibility and stasis. Moreover, it helps to restore the capillaries function by inhibiting the release of inflammatory mediators, decreasing intracapillary pressure and capillary permeability. It also potentiates the action of vitamin C, thus increasing the capillary resistance. The protective effect of diosmin against formation of perivascular edema and its therapeutic application in venous stasis could be attributable to its inhibitory action on inflammatory process or ischemia-induced hyperpermeability, and to its stimulatory effect on the pulsatile activity of lymphatic vessels. Additionally, Diosmin ameliorates the lymphatic drainage by enhancing the intensity and frequency of lymphatic contractions, and this process helps in clearance of accumulated fluids, and hence reducing the edema. Besides, diosmin causes a marked decrease in plasma levels of endothelial adhesion molecules and reduces neutrophil activation, thus providing protection against microcirculatory damage. Overall, these multifaceted actions of diosmin possibly converge to provide maximal benefit to individuals with hemorrhoids (Figure 3).[22-33] There is considerable evidence on the efficacy of diosmin, and several investigators have demonstrated the superior results obtained with micronized form of the molecule.

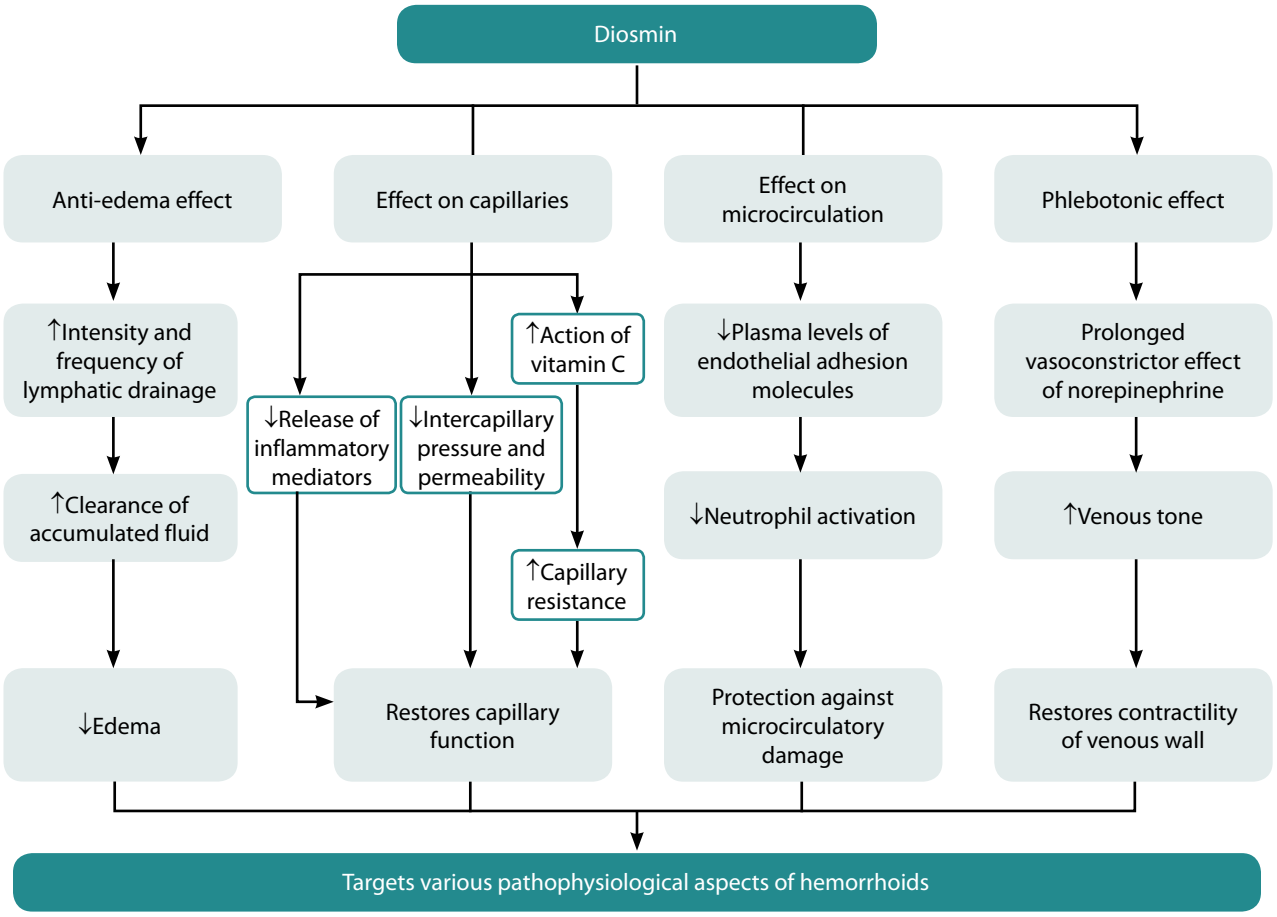
100% Pure Micronized Diosmin: An Edge over Other Agents

The 100% pure form of diosmin would have better absorption and bioavailability, since there will be no flavonoid impurities to competitively decrease the tissue absorption and distribution of this monosubstance. Several evidences support the superior clinical efficacy of micronized diosmin in the management of hemorrhoids. In one such clinical study, investigators showed high effectiveness of the diosmin therapy in patients with hemorrhoids.[20,23]

Micronized purified flavonoid fraction (MPFF) is a variant of the diosmin preparation that which contains various impurities, such as hesperidin, linarin, and isorhoifolin, which can interfere with clinical efficacy of the preparation.[23,34] Moreover, the composition of MPFF has been inconsistent over years, with variations in the product label for MPFF in domestic and international market (90% diosmin and 10% hesperidin). This variation attributable to the additional 10% fraction might cause differences in clinical efficacy and tolerability of different diosmin formulations in patients. In a study, the percentage of patients with no bleeding after five days of treatment with MPFF was approximately 60% only.[35]

Another conservative approach that is often in hemorrhoids treatment is the use of herbal and ayurvedic preparations. However, these preparations have also shown variable efficacy in different individuals. Euphorbia prostrate (indigenously known as Dughdhika) is an ayurvedic preparation that has limited clinical efficacy in hemorrhoids patients with treatment failure of 13%.[36] Moreover, while its exact mode of action in hemorrhoids is not clear, its efficacy in advanced stages of hemorrhoids and in elderly patients is also not well-established. The preparation contains several constituents other than flavonoids, such as phenolic acid and tannins, which could impact the effectiveness of the preparation. Another instance evaluating use of an ayurvedic preparation found that improvement occurred in only 76% of patients even

Figure 3: Mechanism of action of diosmin



after combined use of both tablet and ointment forms of the same ayurvedic composition.[37]

Another venoactive drug calcium dobesilate has also been considered for use in hemorrhoids; however, the drug has limitation in that it does not have comprehensive action on all stages of the venous disorders. A randomized controlled trial showed that calcium dobesilate was not superior to placebo.[38] Furthermore, since it is a category C drug, it cannot be used in women with pregnancy and lactation. Due to reports of agranulocytosis, it has been found to be associated with negative concerns relating to benefit-risk balance.[37]

Overall, the above discussion clearly shows that diosmin is an ideal treatment for hemorrhoids when in its 100% pure form as a monosubstance. A study[20] substantiated the same wherein the role of purified diosmin was evaluated in a group of 66 patients suffering from primitive hemorrhoids of grade 1-4. The results demonstrated the efficacy of purified diosmin in reducing both pain and bleeding; reduction rates of 79% and 67%, respectively, were achieved in the first week of treatment, and 98% and 86%, respectively, in the second week of treatment. In addition, the drug exhibited excellent tolerability (Figure 4).

Similarly, in a placebo-controlled trial,[23] authors reported efficacy of micronized diosmin in significantly improving the duration and/or intensity of individual symptoms of grade 1 or 2 acute internal hemorrhoids. Treatment not only reduced the frequency, duration and/or severity of acute hemorrhoidal symptoms, but improved the overall signs and symptoms of chronic (recurrent) hemorrhoids in comparison to placebo. In all, the efficacy of diosmin is well established in attenuating and treating the symptoms of hemorrhoids. Furthermore, use drug

Figure 4: Efficacy of diosmin therapy in reducing pain and bleeding in patients suffering from hemorrhoids

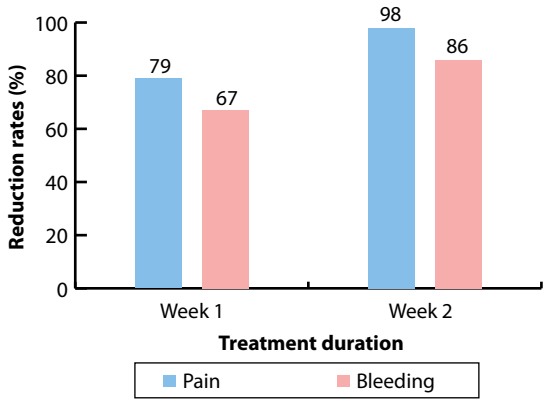
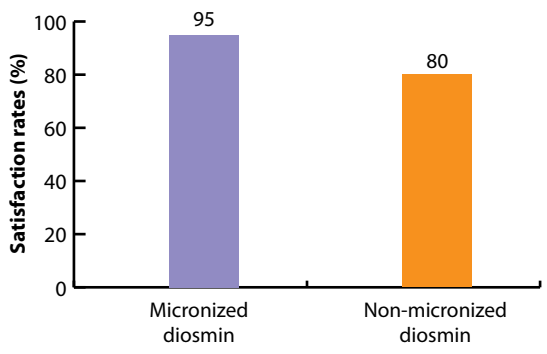


Figure 5: Satisfaction rates among patients with micronized versus non-micronized diosmin therapy



of diosmin in patients referred for surgical therapy may help in reducing the edema and demarcating the area for incision, thereby making surgery convenient with superior outcomes.

Benefits of Micronization

Another approach that is used to enhance the efficacy of Diosmin is the modification of the drug-delivery form, particularly through the process of micronization during the drugs' preparation. Micronization is a significant process used during drugs' preparation to enhance their absorption, and thus efficacy. It is considered that micronization of Diosmin to small particle size of 0.3 microns would facilitate better gastrointestinal absorption of the drug. This in turn would confer improved bioavailability, and the consequent effect would be available in form of enhanced clinical effect.[23,39] Besides, by increasing the absorbed fraction, micronization helps decrease inter-patient pharmacokinetic variability and the influence of exogenous factors, such as diet and dosing regimen.[40]

A randomized, double-blind, multicenter trial[41] involving 90 patients with venous disease of lower limbs assessed the pharmacodynamic and clinical activities of micronized and non-micronized forms of diosmin, and demonstrated statistically significant changes in both groups of patients compared to the baseline values. However, there were remarkably greater improvements in all clinical symptoms and plethysmographic parameters with the micronized in comparison to the non-micronized diosmin. The variable effect was evident in the rates of satisfaction among patients as well; satisfaction rate among patients in micronized diosmin-treated group was 95% while in non-micronized diosmin group it was 80% (Figure 5). Available data also suggest that micronized diosmin is well-tolerated, acceptable, and effective in the treatment of hemorrhoids of pregnancy; the treatment is well-accepted, and does not affect pregnancy, fetal development, birth weight, infant growth and feeding.[42] Thus, micronized form of diosmin offers a myriad of potential therapeutic advantages, and also account for higher satisfaction rates among the patients. Altogether, the efficacy of diosmin is well established in treating and ameliorating the symptoms of hemorrhoids. Furthermore, the micronized form of diosmin offers potential therapeutic advantages and would be favorable to use in patients with hemorrhoids.[23]

Conclusion

Hemorrhoid disease is a common but complex multifaceted disorder. Patients presenting with signs and symptoms of hemorrhoids should be carefully and thoroughly evaluated. There are a multitude of options for the management of hemorrhoids, which range from dietary and lifestyle modification to non-operative and operative treatments. Dietary and lifestyle modification may be the best preventive measures for hemorrhoids. Specific treatment choice should be based on individual patient, the degree and severity of their symptoms as well

as considering their other medical problems. Of note, use of the flavonoid Diosmin has been found to be beneficial across all grades of hemorrhoids. Particularly, the pure micronized form of diosmin could be a first choice of therapy since it is free from other impurities and target possibly all pathophysiological aspects of hemorrhoids. The drug improves venous tone and lymphatic drainage, and reduces capillary hyperpermeability by protecting microcirculation from inflammatory processes.

References

1. Hemorrhoids: an update from pathophysiology to clinical management. Available at https://www.medicographia.com/wp-content/uploads/2019/08/MRX139_whole-issue.pdf. Accessed on 28/02/2020.
2. Sakr M, Saed K. Recent advances in the management of hemorrhoids. *World J Surg Proced.* 2014; 4(3): 55-65.
3. Japanese Practice Guidelines for Anal Disorders I. Hemorrhoids. Available at: http://journal-arc.jp/pdf/001030089.pdf. Accessed on 28/02/2020.
4. Yousefi M, Mahdavi MR, Hosseini SM, *et al.* Clinical Evaluation of Commiphora Mukul, a Botanical resin, in the Management of Hemorrhoids: A randomized controlled trial. *Pharmacogn Mag.* 2013;9(36):350-6.
5. Brown SR. Haemorrhoids: an update on management. *Ther Adv Chronic Dis.* 2017;8(10):141–147.
6. Sun Z, Migaly J. Review of Hemorrhoid Disease: Presentation and Management. *Clin Colon Rectal Surg.* 2016;29(1):22–29.
7. Lohsiriwat V. Treatment of hemorrhoids: A coloproctologist's view. *World J Gastroenterol.* 2015;21(31):9245-9252.
8. Lohsiriwat V. Hemorrhoids: From basic pathophysiology to clinical management. *World J Gastroenterol.* 2012;18(17):2009-2017.
9. Mounsey AL, Halladay J, Sadiq TS. Hemorrhoids. *Am Fam Physician.* 2011;84(2):204-210.
10. Hardy A, Chan CL, Cohen CR. The surgical management of haemorrhoids--a review. *Dig Surg.* 2005;22(1-2):26-33.
11. Cerato MM, Cerato NL, Passos P, *et al.* Surgical treatment of hemorrhoids: A critical appraisal of the current options. *Arq Bras Cir Dig.* 2014;27(1):66-70.
12. Abramowitz L, Weyandt GH, Havlickova B, *et al.* The diagnosis and management of haemorrhoidal disease from a global perspective. *Aliment Pharmacol Ther.* 2010;31 Suppl 1:1-58.
13. Sanchez C, Chinn BT. Hemorrhoids. *Clin Colon Rectal Surg.* 2011;24(1):5 13.
14. Von Roon AC, Reese GE, Tekkis PP. Haemorrhoids: haemorrhoidal artery ligation. *BMJ Clin Evid.* 2009;2009:0415.
15. Schubert MC, Sridhar S, Schade RR, *et al.* What every gastroenterologist needs to know about common anorectal disorders. *World J Gastroenterol.* 2009;15(26):3201-3209.
16. Yeo D, Tan K-Y. Hemorrhoidectomy - making sense of the surgical options. *World J Gastroenterol.* 2014;20(45):16976-16983.
17. Loder PB, Kamm MA, Nicholls RJ, *et al.* Haemorrhoids: pathology, pathophysiology and aetiology. *Br J Surg.* 1994;81(7):946-54.
18. Nisar PJ, Scholefield JH. Managing haemorrhoids. *BMJ.* 2003;327(7419): 847-851.
19. Alonso-Coello P, Mills E, Heels-Ansdell D, *et al.* Fiber for the treatment of hemorrhoids complications: a systematic review and meta-analysis. *Am J Gastroenterol.* 2006; 101(1):181-8.
20. Diana G, Catanzaro M, Ferrara A, *et al.* Activity of purified diosmin in the treatment of hemorrhoids. *Clin Ter.* 2000;151(5):341-4.
21. Gohel MS, Davies AH. Pharmacological agents in the treatment of venous disease: an update of the available evidence. *Curr Vasc Pharmacol.* 2009; 7(3):303-8.
22. Diosmin m-onograph. *Alternative Medicine Review.* 2004;9(3):308-311.
23. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs.* 2003;63(1):71-100.
24. Milano G, Leone S, Fucile C, *et al.* Uncommon serum creatine phosphokinase and lactic dehydrogenase increase during Diosmin therapy: two case reports. *J Med Case Rep.* 2014;8:194.
25. Cova D, De Angelis L, Giavarini F, *et al.* Pharmacokinetics and metabolism of oral diosmin in healthy volunteers. *Int J Clin Pharmacol Ther Toxicol.* 1992;30(1):29-33.
26. Ba-bai-ke-re MM, Huang HG, Re WN, *et al.* How we can improve patients' comfort after Milligan-Morgan open haemorrhoidectomy. *World J Gastroenterol.* 2011;17(11):1448–1456.
27. Araujo D, Viana F, Osswald W. Diosmin therapy alters the in vitro metabolism of noradrenaline by the varicose human saphenous vein. *Pharmacol Res.* 1991;24(3):253-6.
28. Jean T, Bodinier MC. Mediators involved in inflammation: effects of Daflon 500 mg on their release. *Angiology.* 1994;45(6 Pt 2):554-9.
29. Labrid C. Pharmacologic properties of Daflon 500 mg. *Angiology.* 1994;45(6 Pt 2):524-30.
30. Cyrino FZ, Bottino DA, Lerond L, *et al.* Micronization enhances the protective effect of purified flavonoid fraction against postischaemic microvascular injury in the hamster cheek pouch. *Clin Exp Pharmacol Physiol.* 2004;31(3):159-62.
31. Raffetto JD, Khalil RA. Ca^{2+}-Dependent Contraction by the Saponoside Escin in Rat Vena Cava. Implications in Venotonic Treatment of Varicose Veins. *J Vasc Surg.* 2011;54(2):489-496.
32. Srinivasan S, Pari L. Ameliorative effect of diosmin, a citrus flavonoid against streptozotocin-nicotinamide generated oxidative stress induced diabetic rats. *Chem Biol Interact.* 2012;195(1):43-51.
33. Noorafshan A, Karbalay-Doust S, Karimi F. Diosmin reduces calcium oxalate deposition and tissue degeneration in nephrolithiasis in rats: a stereological study. *Korean J Urol.* 2013;54(4):252-7.
34. Rybak Z. Management of lower-limb venous symptoms: what the guidelines tell us. *Medicographia.* 2015;37:50-55.
35. Dimitroulopoulos D, Tsamakidis K, Xinopoulos D, *et al.* Prospective, randomized, controlled, observer-blinded trial of combined infrared photocoagulation and micronized purified flavonoid fraction versus each alone for the treatment of hemorrhoidal disease. *Clin Ther.* 2005; 27(6):746 54.
36. Gupta PJ. The efficacy of Euphorbia prostrata in early grades of symptomatic hemorrhoids – a pilot study. *European Review for Medical and Pharmacological Sciences* 2011;15:199-203.
37. Gupta VK. Haemorrhoids and Conservative Treatment with Pilex. *Haryana Medical Journal.* 1981;2(3):103.
38. Martínez-Zapata MJ, Moreno RM, Gich I, *et al*; Chronic Venous Insufficiency Study Group. A randomized, double-blind multicentre clinical trial comparing the efficacy of calcium dobesilate with placebo in the treatment of chronic venous disease. *Eur J Vasc Endovasc Surg.* 2008;35(3):358-65.
39. Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. *Methods Find Exp Clin Pharmacol.* 1998;20(3):211-5.
40. Garner RC, Garner JV, Gregory S, *et al.* 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(1):32-40.
41. Amato C. Advantage of a micronized flavonoidic fraction (Daflon 500 mg) in comparison with a nonmicronized diosmin. *Angiology.* 1994;45 (6 Pt 2):531-6.
42. Buckshee K, Takkar D, Aggarwal N. Micronized flavonoid therapy in internal hemorrhoids of pregnancy. *Int J Gynaecol Obstet.* 1997; 57(2):145-51.