Hemorrhoid Disease: Role of the Gastroenterologist

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Hemorrhoids: An overview

Hemorrhoids, defined as the symptomatic enlargement and distal displacement of the normal anal cushions, constitute one of the most common anorectal disorders. Hemorrhoids represent a major medical and socioeconomic problem. Available data suggest that about 50% of the population would have encountered hemorrhoids at some point in their life; the peak incidence of this disease for both genders is from 45 to 65 years.[1]

Classification

Hemorrhoids are classified as internal and external depending on whether they are proximal or distal to dentate line. The internal hemorrhoids are further classified, as per Goligher's classification depending upon the degree of prolapse and reducibility, into four grades (Table 1).[2]

Table 1: Grades of internal hemorrhoids

Grade	Characteristic features
I	The mucosa protrudes but does not prolapse
II	The mucosa prolapses on defecation but reduces spontaneously unless thrombosed
III	The mucosa prolapses with minimal provocation and does not reduce spontaneously, rather requires manual reduction
IV	Prolapsed hemorrhoids cannot be reduced

Adapted from: Qureshi W. Hemorrhoid Disease and the Role of the Gastroenterologist. Gastrology and endoscopy news. Jan 2019.

Clinical features of hemorrhoids

Symptoms of external hemorrhoids include pain, bleeding and itching. Drops of bright red blood at the end of a bowel movement or on tissue paper, or blood that coats solid brown stool. Internal hemorrhoids may prolapse and bleed but are painful only when they have thrombosed.[3]

Risk factors

Risk factors for symptomatic hemorrhoids include:[2]

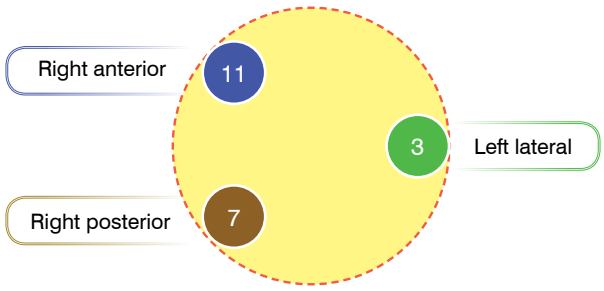
- Low consumption of dietary fiber
- Chronic straining
- Excessive time on the toilet
- Constipation
- Diarrhea
- Pregnancy
- Family history

These risk factors are believed to cause hemorrhoids because increased intraabdominal pressure and hard stools cause obstruction of venous return, which ultimately leads to engorgement of the hemorrhoidal plexus and increases shearing force on the anal cushions.[2]

Pathophysiology

The exact pathophysiology behind hemorrhoids is not well understood. Till now, four theories have been postulated. The sliding anal canal or "cushion theory" is a globally accepted theory.[2] Normally, there are three cushions in the anal canal – located in the right anterior, right posterior and left lateral aspect; along with them some minor cushions are also present in between (Figure 1). The sliding anal canal theory postulates that hemorrhoids develop due to abnormal slippage of cushions through anal canal. In patients with hemorrhoids these anal cushions show remarkable pathological changes that include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibres and fibro elastic tissues, and distortion and rupture of the anal sub epithelial muscle. In addition to that, severe inflammatory reactions are seen in vascular wall and surrounding connective tissue, associated with mucosal ulceration, ischemia and thrombosis.[3]

Figure 1: Sites of major anal cushions



Adapted from: Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. *World J Gastroenterol.* 2012;18(17):2009-2017.

Diagnosis

Rectal bleeding should never be assumed to be from hemorrhoids without at least some type of visual examination. Digital rectal examination, anoscopy, flexible sigmoidoscopy, or colonoscopy should be performed depending on the patient's age, history, presence of alarm symptoms, and risk of colon cancer.[1]

Management of hemorrhoids: A gastroenterologist's perspective

Initial stages of hemorrhoids can be managed with lifestyle modifications that include increasing dietary fiber and oral fluid intake; reducing calorie consumption; regular exercise; improving oral hygiene; abstaining from reading or straining while using the restroom; and avoiding drugs that cause constipation or diarrhea. In addition to that, for symptomatic relief, both topical and oral preparations are used. Topical medications comprise various anesthetics, corticosteroids, or anti-inflammatory medicines. Amongst oral preparations, venotonics such as flavonoids have been used as dietary supplements. Non-surgical procedures are also indicated for grade I and II hemorrhoids along with medical management.[4]

However, in cases of high-grade hemorrhoids or in which non-surgical approaches have failed or complications have occurred, there is a need for surgical intervention. Excisional hemorrhoidectomy is the standard surgical procedure, and a number of minimally invasive procedures have been introduced to reduce post-hemorrhoidectomy pain.[1]

Nonsurgical procedures

For patients not opting for surgery, non-surgical options are also currently available. These procedures are done above the dentate line; hence an anesthetic is not needed. Table 2 illustrates various non-surgical procedures. All of these result in ulceration and fibrous scarring of the proximal internal hemorrhoid complex, which not only prevents blood from flowing into the hemorrhoid but also fixes the distal rectal mucosa to the muscular layer of the colon wall, limiting future prolapse.[2]

> Diosmin exhibits a multifaceted mechanism of action, which includes improvement in venous tone, microcirculation and lymphatic drainage. It effectively targets the pathophysiology of hemorrhoids and can therefore reduce the symptoms of related diseases such as pain, edema and severity

Medical treatment

There are a number of pharmacological therapeutic options, including both topical and oral drugs. There is, however, a paucity of evidence to back up the effectiveness of topical treatments for symptomatic hemorrhoids. In this situation, oral medications like bioflavonoids would seem a sensible choice and might even be the first-line treatment for hemorrhoids. Patients with hemorrhoids have been reported to benefit from bioflavonoids through a number of different mechanisms, including increased lymphatic drainage, decreased venous capacity, decreased capillary permeability, decreased venous tone, and an anti-inflammatory effect. Given that it may affect all pathophysiological features of hemorrhoids, the oral bioflavonoid diosmin has perhaps become a highly effective treatment for hemorrhoids.[5]

Table 2: Non-surgical procedures

Alternatives to surgical excision of hemorrhoids
Rubber band ligation
Infrared coagulation
Direct current electrotherapy
Bipolar diathermy
Sclerotherapy

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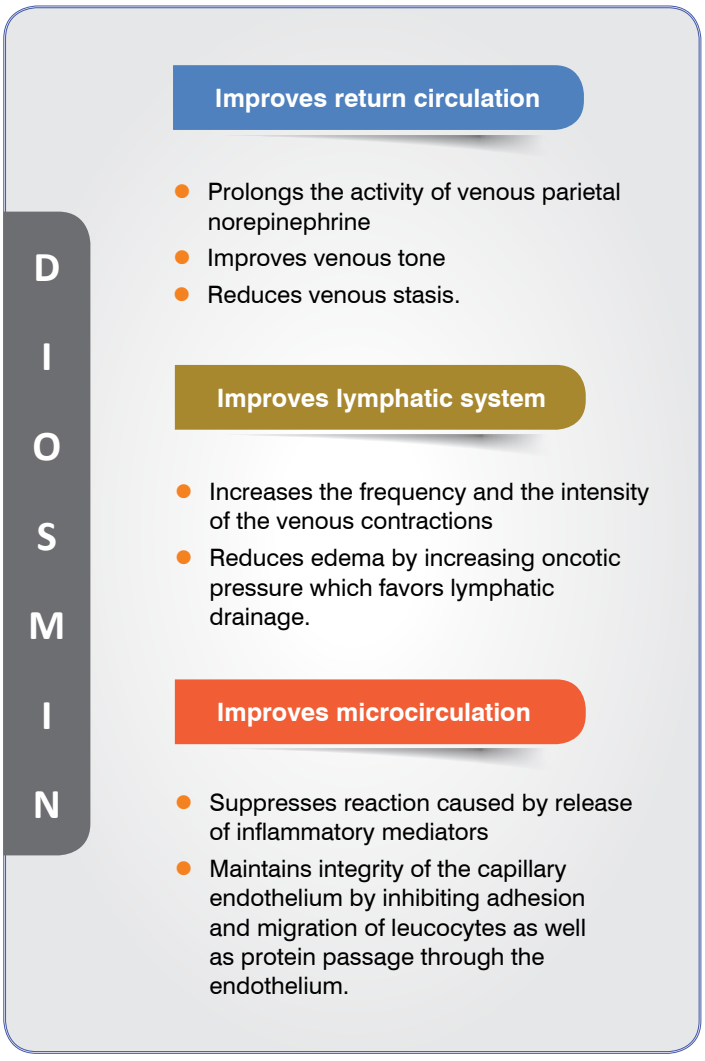


Role of diosmin in hemorrhoids

Diosmin is a naturally occurring flavonoid glycoside, first used as therapeutic agent in 1969. It has vasculoprotective (antiinflammatory and free-radical scavenging) and phlebotonic properties, which justifies its role in treatment of hemorrhoids and chronic venous insufficiency. Diosmin has been used clinically for more than 30 years in the management of variceal dilatations, such as hemorrhoids with good efficacy and safety profile. Diosmin is available in 100% pure form and also in combination with hesperidin, such as micronized purified flavonoid fraction (MPFF). MPFF contains 90% diosmin and 10% hesperidin. Diosmin is extracted from hesperidin and if hesperidin is available in the formulation, it is categorized as an impurity. As per British Pharmacopoeia and US pharmacopoeia, hesperidin is an impurity and its limit should not exceed 5% and 4%, respectively. Hesperidin, if present in the formulation, may compete to bind with the receptors, hence decreasing the efficacy of the formulation and increasing the side effects. 100% pure diosmin brings excellent efficacy in hemorrhoids and other venous diseases.[6-9] Diosmin may be used in conjunction with non-surgical and surgical therapy for hemorrhoids or as an alternative treatment.[10]

Pharmacokinetics

The drug attains maximum plasma concentration after about one hour of administration, and demonstrates a half-life of 26 to 43 hours. Diosmin effectively targets the pathophysiology of hemorrhoids and can therefore reduce the symptoms of related diseases such as pain, edema and severity. In addition, it seems suitable for a conservative approach to hemorrhoids, as it can also affect recurrence.[10]

Mechanism of action

Diosmin exhibits a complex mechanism of action, which includes improvement in venous tone, microcirculation and lymphatic drainage. It enhances venous tone by prolonging the activity of vasoconstrictors, which reduces venous stasis and distensibility of blood vessels. Moreover, it improves microcirculation by inhibiting release of inflammatory mediators. In addition to that, diosmin improves lymphatic drainage by increasing the frequency and intensity of venous contractions, which increase oncotic pressure and hence reducing the edema.[11]

Efficacy of diosmin: Clinical evidences

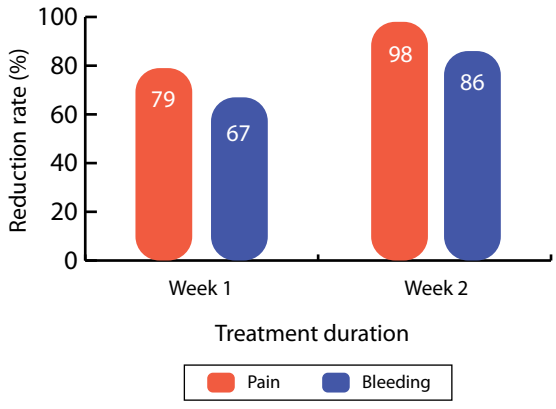
In a Cochrane review,[12] involving 2334 participants [24 randomized controlled trials (RCTs)], phlebotonics were compared with a control in improving the signs, symptoms and severity of hemorrhoids. It was shown that phlebotonics show significant beneficial effects, with improvement in outcomes of pruritus, bleeding, discharge, leakage, and overall symptom improvement.

Venoactive drugs, such as micronized purified flavonoid fraction (MPFF), have been used to treat haemorrhoid. Micronized purified flavonoid fraction (MPFF) is a variant of the diosmin preparation that contains various impurities, such as hesperidin, linarin, and isorhoifolin, which can interfere with clinical efficacy of the preparation. Flavonoid impurities decrease the tissue absorption and distribution of diosmin.[13]

The 100% pure form of diosmin would have better absorption and bioavailability. In one such clinical study,[6] Investigators showed high effectiveness of the diosmin therapy in patients with hemorrhoids. The study evaluated the role of purified diosmin in a group of 66 patients suffering from hemorrhoids (grade I-IV). The results demonstrated significant reduction in both pain and bleeding. The reduction rate was 79% and 67% respectively, in the first week of treatment, and 98% and 86% respectively, in the second week of treatment (Figure 2). Moreover, the drug exhibited excellent tolerability.

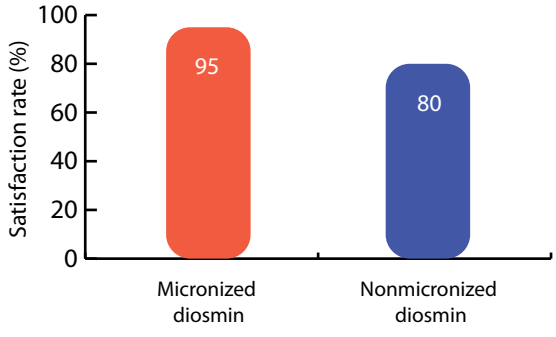
Similarly, in a placebo-controlled trial,[14] authors reported efficacy of micronized diosmin in significantly improving the duration and/ or intensity of individual symptoms of grade I or II acute internal hemorrhoids. Treatment not only reduced the frequency, duration and/or severity of acute hemorrhoidal 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.

Figure 2: Efficacy of diosmin therapy in reducing pain and bleeding



Adapted from: Diana G, Catanzaro M, Ferrara A, *et al.* Activity of purified diosmin in the treatment of hemorrhoids. *Clin Ter.* 2000;151(5):341-4.

Figure 3: Satisfaction rate among patients with micronized versus non-micronized diosmin



Adapted from: Amato C. Advantage of a micronized flavonoidic fraction (Daflon 500 mg) in comparison with a nonmicronizeddiosmin. *Angiology.* 1994;45 (6 Pt 2):531-6.

Benefits of micronization

Micronization of diosmin to small particle size of 0.3 microns would facilitate better gastrointestinal absorption of the drug. In addition to increasing the rate of adsorption, micronization helps reduce pharmacokinetic fluctuations between patients and the effects of extrinsic factors such as diet and dosing regimen. A randomized, double-blind,[15] multicenter trial involving 90 patients with venous disease of lower limbs showed remarkably greater improvement in all clinical symptoms and plethysmographic parameters with the micronized in comparison to the non-micronized diosmin. Satisfaction rate among patients in micronized diosmin-treated group was 95% while in non-micronized diosmin group it was 80% (Figure 3).

The available data also suggest that micronized diosmin is tolerable, acceptable and effective in the treatment of gestational hemorrhoids. This treatment is widely accepted and does not affect pregnancy, fetal development, birth weight, infant growth or nutrition.[16] Therefore, the micronized form of diosmin provides a variety of potential therapeutic benefits and also contributes to higher patient satisfaction. Overall, the effectiveness of diosmin in the treatment and alleviation of hemorrhoidal symptoms is well established. In addition, the micronized form of diosmin will provide potential therapeutic benefits and will be beneficial for use in patients with hemorrhoids.

Conclusion

Gastroenterologists offer an effective alternative to hemorrhoid management in the form of non-surgical treatment along with medical treatment. In medical treatment, the 100% purified micronized diosmin preparation offers therapeutic advantage through better absorption and bioavailability. It is an ideal treatment for hemorrhoids. Moreover, micronized diosmin is tolerable, acceptable and effective in the treatment of gestational hemorrhoids. Furthermore, use 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.

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