

REVIEW

Hemorrhoid management in women: the role of tribenoside + lidocaine

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Abstract

Hemorrhoids are commonly reported in women. However, despite the high prevalence of hemorrhoids in women and the major impact of this condition on quality of life, specific evidence and recommendations on the treatment of hemorrhoids in women are scant. This paper reviews various options in current therapy for hemorrhoids in women—namely, medical intervention (topical and systemic drug therapy)—and discusses the available clinical evidence for an appropriate use of over-the-counter topical formulations for the symptomatic treatment of hemorrhoids. Its focus is on a medical preparation containing tribenoside + lidocaine, available as a rectal cream (tribenoside 5%/lidocaine 2%) and a suppository (tribenoside 400 mg/lidocaine 40 mg) and marketed under the brand Procto-Glyvenol® (Recordati, SpA, Italy). Given its rapid comprehensive efficacy on all the different symptoms of hemorrhoids, the tribenoside + lidocaine combination can find a place in the treatment of this hemorrhoidal disease. Importantly, its efficacy and

tolerability have been formally evaluated in several well-conducted studies, some of which were specifically conducted in women. In particular, tribenoside + lidocaine can be safely administered in postpartum women and in pregnant women after the first trimester of pregnancy. In pregnant women, the tribenoside/lidocaine combination significantly improved both subjective and objective symptoms of hemorrhoids. Fast onset of symptom relief was reported from 10 minutes after administration, lasting up to 10–12 hours. On these bases, tribenoside + lidocaine can represent a fast, effective, and safe option to treat hemorrhoids when conservative therapy is indicated, and it deserves consideration as a first-line treatment of this disease in clinical practice.

Keywords: hemorrhoids, lidocaine, tribenoside, women's medicine.

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Introduction

Hemorrhoids affect approximately 25% of the general population in their lifetime and are associated with several bothersome symptoms, such as painful defecation, itching with the urge to scratch, and bleeding, which in turn limit social activities and have a major impact on quality of life.^{1–3} The severity of hemorrhoids is classified into four stages, according to Goligher's classification (Table 1). More advanced stages of the disease require surgical treatment, while medical management and lifestyle interventions are suitable for grade I/II hemorrhoids, which represent the wide majority (>90%) of all reported cases. Remarkably, many patients experience hemorrhoids without seeking medical consultation because of embarrassment or fear, discomfort, and pain associated with the treatment.⁴

In particular, hemorrhoids are commonly reported in women, mostly during pregnancy and postpartum.⁵ Pregnancy and

vaginal birth predispose women to develop symptomatic hemorrhoids for several reasons: hormonal changes, increased intra-abdominal pressure, straining during defecation due to constipation, prolonged straining during the second stage of labor for more than 20 minutes, and giving birth to a baby with a weight over 3800 g.⁶ The high levels of progesterone during pregnancy decrease the strength of the muscles' venous walls and reduce the venous tone; any combination of increased intra-abdominal pressure, increased venous congestion from the weight of the fetus, and obstruction of venous returns contribute to the development of pathological changes and incidence of hemorrhoids. Women with this condition may ultimately experience anal incontinence, and also report difficulties in dealing with hygienic problems.⁶ Of note, women may perceive hemorrhoids as an embarrassing and sensitive disease, with a consequent reluctance to ask for medical attention.⁶ Despite the high prevalence of hemorrhoids in women and the major

Table 1. Hemorrhoid grading according to Goligher's classification.

Hemorrhoid degree	Features
Grade I	The anal cushions bleed but do not prolapse.
Grade II	The anal cushions prolapse through the anus on straining but reduce spontaneously.
Grade III	The anal cushions prolapse through the anus on straining or exertion and require manual replacement into the anal canal.
Grade IV	The prolapse stays out at all times and is irreducible. Acutely thrombosed, incarcerated internal hemorrhoids and incarcerated, thrombosed hemorrhoids involving circumferential rectal mucosal prolapse are also fourth-degree hemorrhoids.

impact of this condition on quality of life, specific evidence and recommendations on the treatment of hemorrhoids in women are scant.⁵ This paper discusses current options in the therapy for hemorrhoids in women—namely, medical intervention (topical and systemic drug therapy)—and discusses the available clinical evidence for an appropriate use of over-the-counter topical formulations for the symptomatic treatment of hemorrhoids with a focus on the combination of tribenoside + lidocaine, which has been demonstrated to be a fast, effective, and tolerated option for the local treatment of low-grade hemorrhoids.⁷

Selection of evidence

Papers considered for this review were retrieved by a PubMed search, using different combinations of pertinent keywords (e.g., tribenoside and hemorrhoids), without any limitations on publication date or language. Documents from the authors' personal collection of literature could also be considered. Papers were selected for inclusion according to their relevance for the topic, as judged by the author.

Management of hemorrhoids in women: state of the art

In women with hemorrhoids, symptoms include pain, itching, and intermittent bleeding from the anus; quality of life can vary from mild physical and psychological discomfort to difficulty in dealing with everyday activities, depending on the severity of pain.^{6,8}

As hemorrhoids are such a common condition in women and can be associated with both physical symptoms and quality-of-life impairment, prevention is crucial. Dietary modification consisting of adequate fluid and fiber intake represents the primary approach to patients at high risk of hemorrhoid disease.⁹

In patients with overt hemorrhoids, hygienic and dietary measures should be taken to prevent constipation, with the aim of maintaining soft, bulked stools that pass easily without straining during defecation.⁹ A diet high in fibers, approximately 20–35 g/day, or intake of fiber supplements, such as maltodextrin-resistant fruit oligosaccharides, psyllium, methylcellulose, or calcium polycarbophil can be recommended. There have been several randomized controlled trials (RCTs) studying the relationship between dietary fiber and constipation. Some studies reported that dietary fiber can increase stool frequency, improve stool consistency, and have no obviously adverse effects. However, in another study, dietary fiber was not found more effective than placebo in therapeutic success, and it might increase the frequency of abdominal pain. Furthermore, large trials examining the effect of dietary fiber in the treatment of constipation are needed, the possible influential factors should be considered, and more gastrointestinal symptoms and adverse events should be reported before dietary fiber is formally recommended.¹⁰

In addition to a high-fiber diet, it is also important to increase fluid intake, which adds moisture to stool, thus reducing constipation. Of note, no studies have been published so far showing that increasing liquid volume is effective as a treatment in euhydrated subjects with chronic constipation. Nevertheless, inadequate fluid intake or excessive fluid loss from diarrhea, vomiting, or febrile illness may cause hardening of the stool and is considered to be an important cause of constipation, especially in infants.¹¹ Increasing liquid intake is commonly recommended for constipated children, adults, and elderly subjects. Although the effects of fluid intake on constipation have never been fully studied or understood, the recommendation has remained mostly out of tradition.¹²

Finally, the use of polyethylene glycol (PEG/macrogol 4000), an osmotic laxative, can also be considered a safe and effective treatment, even during pregnancy. In this respect PEG/macrogol should be considered a first-line option, due to its minimal absorption and elimination in the urine without being metabolized.¹³ Lastly, moisturizing and cleansing wipes can be used as a replacement for toilet paper by providing a cool, soothing sensation around the back passage.¹⁴ Formulations (either wipes or intimate soap/gel) containing extract of *Ruscus aculeatus*, well known for its soothing properties, and devoid of alcohol, can provide relief for people suffering from hemorrhoids. Extract of *Ruscus aculeatus* has been documented to be effective in increasing venous tone because of its anti-inflammatory and astringent properties.¹⁵

Conservative measures with local treatment are also recommended, while surgical procedures should be indicated only in case of failure of conservative treatment or high-grade disease.^{16,17} As stated by the American Society of Colon and Rectal Surgeons (ASCRS) guidelines, medical therapy for hemorrhoids is based upon a heterogeneous group of options that can be offered with expectations of minimal harm and a decent potential for relief.^{9,18}

Current medical preparations are available as topical creams, ointments, gels, lotions, suppositories, and pads. These preparations may contain various ingredients, such as local anesthetics, corticosteroids, vasoconstrictors, antiseptics, keratolytics, protectants (e.g., mineral oils, cocoa butter), and astringents (ingredients that cause coagulation, e.g., witch hazel).¹⁹

Clinicians should educate patients to use only medications whose efficacy and safety, including in special conditions (e.g., pregnancy), have been firmly established.^{19–21}

As inflammation plays an important role especially in the cutaneous symptoms of hemorrhoidal disease,²² topical antihemorrhoidal preparations containing an anti-inflammatory agent and a local anesthetic are extensively used, and their use is supported by current medical practice.¹⁹ Some commonly used combinations include ketocaine/fluocinolone and hydrocortisone/benzocaine. Corticosteroids can be effective in this scenario; however, these molecules, often available as prodrugs, may be associated with a risk of systemic adsorption being systemically absorbed, distributed, metabolized, and excreted. Thus, their higher lipophilicity may limit their application over the middle-term period or in women who are elderly, are breastfeeding, or are pregnant.

Accordingly, topical formulations providing alternatives to corticosteroids, but still endowed with anti-inflammatory and wound-healing effects, are highly desirable for adequate control of both objective and subjective symptoms of hemorrhoids. The topical combination of tribenoside and lidocaine (marketed under the brand Procto-Glyvenol[®], Recordati SpA, Italy) addresses the aforementioned criteria along with a formal and robust evaluation of its efficacy and safety in a number of well-conducted studies, most of which included a comparator arm using a reference treatment for grade I and II of hemorrhoids—that is, steroid-based preparations (hydrocortisone, prednisolone, fluocortolone) as recently reviewed.⁷ Tribenoside + lidocaine combines the rapid local anesthetic action exerted by lidocaine with the efficacy of tribenoside in reducing inflammation, promoting local healing, and favoring the recovery of local vessels to normal conditions. This double mechanism of action allows to control both subjective (e.g., pain and discomfort) and objective (e.g., prolapse and bleeding) symptoms of hemorrhoids.

In addition to the topical remedies, preparations for oral use including vasoactive ingredients have been proven to be effective. Based on the experience of their efficacy in the

treatment of chronic venous insufficiency, phlebotonic drugs for oral use have largely been prescribed to treat hemorrhoids and are supported by well-grounded evidence.^{9,23–25} Phlebotonics are a heterogeneous class of drugs consisting of plant extracts (i.e., flavonoids) and synthetic compounds (i.e., calcium dobesilate). Although their precise mechanism of action has not been fully established, they are known to improve venous tone, stabilize capillary permeability, and increase lymphatic drainage. The evidence suggests that there is a potential benefit in using phlebotonics in treating hemorrhoidal disease as well as a benefit in alleviating post-hemorrhoidectomy symptoms. Outcomes, such as bleeding and overall symptom improvement, show a statistically significant beneficial effect, and there were few concerns regarding their overall safety from the evidence presented in the clinical trials.²⁶ In particular, diosmin shows anti-inflammatory and antioxidant activities, phlebotonic and vasoactive effects, improving venous tone, lymphatic drainage, and capillary hyperpermeability.²⁷ A new micronized diosmin formulation has been recently developed to increase bioavailability for the treatment of hemorrhoids.²⁸ Ginkgo-based preparations including extract from the *Ginkgo biloba* tree (e.g., Ginkor brand) are also used as an oral supplement.²⁹

Tribenoside + lidocaine: an effective and well-tolerated combination therapy

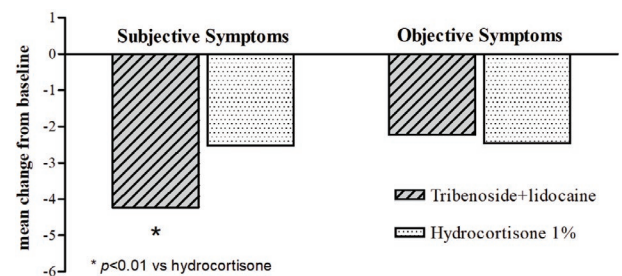
Tribenoside + lidocaine combination is a medical preparation for the local treatment of hemorrhoids, delivered as a suppository or rectal cream (Procto-Glyvenol[®]). This combination offers a rapid and comprehensive efficacy on all different symptoms of hemorrhoids thanks to the pharmacological peculiarities of its single components, the saccharide tribenoside and the fast-acting anesthetic lidocaine. Tribenoside possesses a wide spectrum of activities including anti-inflammatory, mild analgesic, antitoxic, wound-healing, fibrinolysis-promoting, antiarthritic, membrane-stabilizing, and venotropic properties along with a relevant tolerability profile toward the gastrointestinal and immune systems.³⁰ Importantly, the aforementioned activities differentiate tribenoside from the standard treatment of hemorrhoids—that is, topical corticosteroids—thus, strengthening its place in therapy in the local treatment of hemorrhoids, providing comparable efficacy in reducing the associated inflammation and better tolerability than corticosteroids.^{7,30} The combination with lidocaine confers an additional benefit (e.g., the fast relief from pain and itching), which is desirable during the acute phase of a hemorrhoidal crisis to help patients cope better with the most bothersome complaints, including itching. Therefore, tribenoside + lidocaine can improve both objective symptoms (inflammation, hemorrhage, secretion), thanks to the presence of tribenoside, and subjective symptoms (pain, itching, sense of weight, and tenesmus), given the local action of lidocaine.⁷

The clinical evidence of tribenoside + lidocaine efficacy and tolerability stems from several clinical studies conducted in over 1200 patients of either gender, either *versus* its two individual components or *versus* steroids in the same setting as previously described.^{7,31–41} The studies investigated both formulations of tribenoside + lidocaine combinations (suppositories and cream) either within the same study design or in distinct trials. Most importantly, the combination was compared and contrasted with active comparators and the treatment duration ranged between 10 and 28 days to investigate long-term tolerability. A detailed description of available studies goes beyond the aims of this review and can be found elsewhere.⁷ Here, we focus only on studies specifically conducted on women or those involving a wide majority of women among their participants. However, all studies enrolled a large population of women treated with tribenoside + lidocaine; safety was reported as subjective evaluation by the study investigators being excellent in all cases. Of note, rare reported adverse reactions during treatment can be local reactions, such as burning (application site pain), rash, and pruritus.⁴²

Moggian and colleagues conducted two controlled, double-blind studies, published in a single paper, evaluating 67 women (mean age: 33 years) with hemorrhoidal disease as a consequence of pregnancy or delivery (either internal or external or mixed hemorrhoids).³³ In one study, tribenoside 400 mg + lidocaine 40 mg suppositories (n=21) administered twice daily for up to 10 days was compared with lidocaine 40 mg only (n=20). In the parallel double-blind evaluation, tribenoside + lidocaine suppositories (n=13) were compared with suppositories of hydrocortisone 1% (n=13).³³ Clinical evaluation of objective (secretion, hemorrhage, nodules) and subjective (pain, burning, pruritus) symptoms was assessed by a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Mean total scores for objective or subjective symptoms were calculated by adding the means of each symptom scores, and the differences between treatments were analyzed by a nonparametric test. Tribenoside + lidocaine suppositories improved both subjective (mean score at baseline: 4.62; mean score after treatment: 0.24; $p<0.01$) and objective (2.86 *versus* 0.91; $p<0.01$) symptoms, while patients on lidocaine only experienced a relief of subjective symptoms (5.75 *versus* 3.25; $p<0.01$). Remarkably, tribenoside + lidocaine was more effective than hydrocortisone in the improvement of subjective symptoms (tribenoside + lidocaine: -4.23 *versus* baseline; steroids: -2.53 *versus* baseline; $p<0.01$) (Figure 1). The tolerability of tribenoside + lidocaine was evaluated by the investigators being “very good” in all cases.

Delarue and colleagues evaluated the effectiveness and safety of tribenoside + lidocaine during pregnancy and postpartum. In total, 40 women with hemorrhoids as a consequence of pregnancy (n=33) or delivery (n=7) were treated with oral tribenoside 400 mg 2–6 times daily for 10 days (postpartum) or 20 days (pregnancy).³⁸ Local treatment with tribenoside +

Figure 1. Improvement of subjective and objective symptoms of hemorrhoids with tribenoside + lidocaine and hydrocortisone containing preparation in 26 women with hemorrhoidal disease as a consequence of pregnancy or delivery, expressed as difference in the score reported after treatment and the score reported at baseline. $p<0.001$ for both preparations *versus* baseline; $p<0.01$ for tribenoside + lidocaine *versus* hydrocortisone 1% in the effect on subjective symptoms. Graphical elaboration of data in Moggian.³³



lidocaine suppositories twice daily was administered for 5 days in 19 women who complained of bothersome pain. Although the open-label study design may provide biased results, 15 patients were satisfied with the treatment, 18 were moderately satisfied, and only 7 patients were poorly satisfied. Nevertheless, positive results were reported in 82.5% of cases, and a fast onset of symptom relief was reported when suppositories were administered (10 minutes to 1 hour). Tolerability was considered very good in all patients: no systemic or local adverse effects were observed.

Lastly, a long-term, open-label study was carried out by Zurita-Briceno in 30 patients (25 women) who were treated with tribenoside + lidocaine suppositories three times daily for 4 weeks. Efficacy was judged as “excellent” or “good” by over 80% of patients with very few adverse events, all not related to treatment.⁴¹

Conclusions and place in therapy

Hemorrhoids are a common condition. A large number of over-the-counter products are available on the market to address the prevalent attitude of patients to prefer to self-medicate over medical consultation.¹

The standard treatment is with steroids, but they are unfortunately burdened by an unbalanced benefit/risk ratio that hampers their usefulness,^{18,43} thus limiting their therapeutic potential in some special populations, such as pregnant/breastfeeding women or the elderly. Given its rapid comprehensive efficacy on all different symptoms of

hemorrhoids, the tribenoside + lidocaine combination can find a place in the treatment of this hemorrhoidal disease. Importantly, its efficacy and safety have been formally evaluated in several well-conducted studies, most of which included a comparator arm, either semiplaceto preparations containing either monocomponents (only lidocaine or only tribenoside) or steroid-containing preparations. No data *versus* placebo or vehicle are available.

Overall, the combination of tribenoside + lidocaine was found to be superior over the single components in symptoms improvement, likely due to its ability to ameliorate both subjective and objective symptoms at the same time. The effects on subjective symptoms were rapidly observed after the administration of the combination (i.e., 10–30 minutes).³¹ Moreover, the combination of tribenoside + lidocaine was at least equally effective as the gold-standard treatment for hemorrhoids—that is, steroid-based preparations—and

sometimes superior in providing a prompt relief of bothersome symptoms, such as pain and itching. Finally, tolerability was excellent in all available studies with only negligible adverse events being reported.⁷ It is noteworthy that this combination can be particularly suitable for some populations of patients at high risk of hemorrhoids in whom steroids could be contraindicated. In particular, tribenoside + lidocaine can be safely administered in postpartum women and in pregnant women after the first trimester of pregnancy (although no randomized studies have been conducted in this specific population). In addition, the combination of tribenoside + lidocaine can be suitable in athletes for whom rectal steroids are prohibited.

In conclusion, tribenoside + lidocaine may represent a fast, effective, and safe option to treat hemorrhoids when conservative therapy is indicated, and it deserves consideration as first-line treatment of this disease in clinical practice.

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