

Tribenoside and lidocaine in the local treatment of hemorrhoids: an overview of clinical evidence

Z. LORENC¹, Ö. GÖKÇE²

¹General, Colorectal and Trauma Surgery Silesian Medical University Katowice, Poland

²Department of Surgery, Yeditepe University, Istanbul, Turkey

Abstract. – OBJECTIVE: The combination of tribenoside+lidocaine (Procto-Glyvenol®) is a medical preparation for the local treatment of hemorrhoids, delivered as a suppository or rectal cream. This product has been used for decades in the therapy of hemorrhoids. This review discusses available evidence on the use of tribenoside/lidocaine in clinical practice.

MATERIALS AND METHODS: Papers were retrieved by a PubMed search, using different combinations of pertinent keywords (e.g. tribenoside AND hemorrhoids), without any limitations in terms of publication date and language. Documents from 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 Authors.

RESULTS: The efficacy of the combination of tribenoside+lidocaine in relieving symptoms caused by hemorrhoids and its safety have been assessed in several clinical studies on patients of either gender, either versus its two individual components (tribenoside and lidocaine) or versus steroids in the same setting. Five studies compared the combination treatment with each of its single components, and of these, three studies compared tribenoside+lidocaine with a tribenoside-free semi-placebo preparation containing only lidocaine, and two studies compared this combination with lidocaine-free preparations containing only tribenoside. Tribenoside+lidocaine was compared with steroid-containing preparations in six studies. Last, two studies evaluated the efficacy and tolerability of the tribenoside+lidocaine combination in women with hemorrhoids as a consequence of pregnancy or delivery.

All the above-mentioned studies were well-conducted and can provide a comprehensive evaluation of tribenoside+lidocaine in the treatment of hemorrhoids.

CONCLUSIONS: Enough evidence exists to recommend the use of this combination therapy as a fast, effective and safe option for the local treatment of low-grade hemorrhoids.

Key Words:

Tribenoside, Lidocaine, Hemorrhoids.

Introduction

Hemorrhoid disease is one of the most common proctological conditions in Western countries¹. Its prevalence is as high as 36% of the general population, with a higher incidence in middle-aged people of high socioeconomic status^{1,2}. It has been estimated that about 50% of the general population will experience symptomatic hemorrhoids at some points in their life³. In addition, pregnant women are at high risk of developing hemorrhoid disease^{4,5}. The prevalence of hemorrhoids in pregnant woman ranges from 25% to 35%, and up to 85% of pregnant women experience hemorrhoids in the third trimester⁶. Other subjects at particular risk of developing hemorrhoids are elderly and those with high body mass index^{7,8}.

For what concerns clinical presentation and symptoms, hemorrhoids can cause anal discharge and itching. Moreover, internal hemorrhoids may cause objective symptoms such as prolapse or rectal bleeding, while external hemorrhoids can result in subjective symptoms including pain, burning and itching due to engorgement and thrombosis⁹.

The severity of hemorrhoids is classified into four stages, according to Goligher¹⁰. More advanced stages of 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^{1,8,9}.

In particular, dietary and lifestyle changes, which require a high patient compliance, are usually considered the first step for any conservative

strategy; however, evidence supporting these interventions is anecdotal¹. Fiber supplementation can play a role as a supportive treatment of hemorrhoids, in particular as stool softeners, when combined with other therapies^{11,12}. Phytotherapy has been widely tested for the therapy of low-grade disease, but studies supporting these interventions are of modest methodological quality¹. Medical treatment is mainly based on the use of topical preparations, containing anti-inflammatory drugs including steroids, anesthetics, astringents, and/or antiseptics⁹. However, in most cases no randomized trials have been conducted to assess the efficacy and safety of different interventions which in some cases – e.g., steroids – are associated with the potential onset of adverse events^{1,9}.

The combination of tribenoside+lidocaine (Procto-Glyvenol[®], Recordati, Italy) is a medical preparation for the local treatment of hemorrhoids, delivered as a suppository or rectal cream¹³. This product has been used for decades in the therapy of hemorrhoids, and its efficacy and safety are supported by a number of well-conducted studies and broad clinical experience.

This review discusses available evidence on the use of tribenoside/lidocaine in patients with hemorrhoids.

Selection of Evidence

Papers for consideration for the present review were retrieved by a PubMed search, using different combinations of pertinent keywords (e.g. tribenoside AND hemorrhoids), without any limitations in terms of publication date and language. Documents from 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 Authors.

Clinical Pharmacology

Tribenoside is a saccharide derivative which has been extensively used for the treatment of hemorrhoids¹⁴. Several studies have shown that tribenoside possesses a unique spectrum of pharmacological activities, and in particular anti-inflammatory, mild analgesic, antitoxic, wound-healing, fibrinolysis-promoting, anti-arthritis, amine-release-inhibitory, membrane-stabilizing and venotropic properties have been reported¹⁵. Noteworthy, unlike corticosteroids or nonsteroidal anti-inflammatory agents, tribenoside does not present untoward effects on the gastrointestinal system, the connective tissue or the immune system, and does not affect the prostaglandin-synthetase

system. Tribenoside seems to share the positive pharmacological properties ascribed to glucocorticoids and non-steroidal anti-inflammatory agents, yet is free from the undesirable effects on the gastro-intestinal system, the connective tissue or the body's defence system¹⁵. Remarkably, tribenoside exhibits anticoagulant and inhibitory activity against inflammatory mediators such as histamine and prostaglandins, thus providing benefit to microcirculation, reducing capillary permeability and improving vascular tone¹⁴. An *in vitro* study, specifically aimed at investigating the molecular bases of the efficacy of tribenoside in the treatment of hemorrhoids, showed that the expression of laminin $\alpha 5$, a major component of the basement membrane disrupted in this disease, was four times higher in the tribenoside-treated cells than in controls¹⁴. Collectively, these findings suggest that tribenoside interacts with epidermal cells and regulates the expression and localization of laminins, thus helping reconstruct basement membrane in wound healing of hemorrhoids.

On the other hand, lidocaine is a widely-used local anesthetic which relieves pain, burning and itching caused by hemorrhoids^{1,16}. This molecule is characterized by a fast (few minutes) onset of its surface anesthetic action, providing rapid relief from pain and itching¹⁶.

Therefore, this combination therapy combines the rapid local anesthetic action exerted by lidocaine with the efficacy of tribenoside in 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 reducing inflammation and improving vascular tone.

Overview of Clinical Evidence

The efficacy of the combination of tribenoside+lidocaine in relieving symptoms caused by hemorrhoids and its safety have been assessed in several clinical studies on patients of either gender, either versus its two individual components (tribenoside and lidocaine) or versus steroids in the same setting¹⁷⁻²⁷.

Table I provides an overview of those studies. Of note, 5 studies compared the combination treatment with each of its single components. Of these, 3 studies compared tribenoside+lidocaine with a tribenoside-free semi-placebo preparation containing only lidocaine¹⁷⁻¹⁹, and 2 studies compared this combination with lidocaine-free preparations con-

Table 1. Overview of the identified studies on the combination of tribenoside + lidocaine (TL).

Study	Design	Total number of patients	Treatment	Main outcomes
Rizzi et al ¹⁷ Analysis of 4 different studies:	<p>I. Double blind study comparing TL cream with semi-placebo cream with lidocaine only</p> <p>II. Open label analysis on TL cream only</p> <p>III. Open-label analysis on TL suppositories</p> <p>IV. TL vs. steroid-containing preparations</p>	<p>177</p> <p>I. 28</p> <p>II. 60</p> <p>III. 44</p> <p>IV. 45</p>	<p>All applied up to 10 days:</p> <p>I. Tribenoside 5% + lidocaine 2% cream vs. lidocaine 2%</p> <p>II. Tribenoside 5% + lidocaine 2% cream</p> <p>III. Tribenoside 400 mg + lidocaine 40 mg suppositories</p> <p>IV. Tribenoside 400 mg + lidocaine 40 mg suppositories vs. hydrocortisone or triamcinolone or fluocortolone or prednisolone</p>	<ul style="list-style-type: none"> • Clinical efficacy rated as “good” in 13 patients on tribenoside + lidocaine, compared with 4 patients on lidocaine only ($p<0.01$). • Treatment was judged as “ineffective” in no patients on TL, vs. 4 subjects in the other group ($p<0.01$). • Both formulations of TL resulted in a rapid (about 30 mins) symptom improvement • TL was significantly preferred over steroids ($p<0.001$) • TL was significantly superior over lidocaine in providing rapid relief on both subjective and objective symptoms ($p=0.01$). • Clinical efficacy was rated as “very good local and systemic tolerability” in 15 patients on TL and 3 subjects on lidocaine ($p=0.01$). • TL had very good local and systemic tolerability • TL significantly improved both subjective and objective symptoms, while lidocaine resulted in an improvement of subjective symptoms only. • Significantly more effective improvement of subjective symptoms with TL compared with steroid. • Excellent tolerability.
Fontana et al ¹⁸	<p>Randomized, double-blind study vs. lidocaine</p> <p>Analysis of two different studies:</p> <p>I. Randomized, double-blind study of TL suppositories vs. lidocaine only</p> <p>II. Randomized, double-blind study of TL suppositories vs. hydrocortisone</p>	<p>48</p> <p>67 women</p>	<p>Tribenoside 5% and lidocaine 2% cream versus semi-placebo cream containing lidocaine 2% for up to 10 days</p> <p>I. Tribenoside 400 mg + lidocaine 40 mg suppositories vs. lidocaine 40 mg only for up to 10 days</p> <p>II. Tribenoside 400 mg + lidocaine 40 mg suppositories vs. hydrocortisone 1% up to 10 days</p>	<ul style="list-style-type: none"> • TL significantly improved both subjective and objective symptoms, while lidocaine resulted in an improvement of subjective symptoms only. • Significantly more effective improvement of subjective symptoms with TL compared with steroid. • Excellent tolerability.

Continued

Table 1. Overview of the identified studies on the combination of tribenoside + lidocaine (TL).

Study	Design	Total number of patients	Treatment	Main outcomes
Marques et al ²⁰	Randomized, double-blind study	462	TL (cream or suppository) vs. tribenoside alone, prednisolone trimethylacetate 0.1% + vioform 5% or fluocinolone acetonide 0.01% + bismuth gallate 5% + lidocaine 2%	<ul style="list-style-type: none"> • Similar efficacy of the four preparations • Use of TL recommended thanks to its favorable safety profile and its rapid and effective action.
Angriman et al ²¹	Single-blind study	40	TL cream, tribenoside 5% cream, prednisolone pivalate 0.1% + vioform 5% cream, and fluocinolone acetonide 0.01% + lidocaine 2% cream. All treatments were administered for up to 10 days	<ul style="list-style-type: none"> • Similar efficacy of the different preparations. • No adverse events reported with TL
Berson et al ²²	Double-blind study	289	Tribenoside 400 mg + lidocaine 40 mg suppositories vs. prednisolone suppositories for up to 14 days	<ul style="list-style-type: none"> • A trend to an advantage in terms of nodules improvement was observed for TL. • For both groups, treatment effect was rated as “Good” by the majority of patients and physicians. • Faster onset of action with TL. • Good tolerability of TL.
Holzer ²³	Randomized, double-blind study	52	Tribenoside + lidocaine suppositories (400/40 mg bid) or cream (5%/2% mg) versus hydrocortisone-containing preparation, either as cream or suppositories	<ul style="list-style-type: none"> • Similar efficacy of the two preparations. • Adverse events associated with steroids potentially avoided with TL.

Continued

Table 1. Overview of the identified studies on the combination of tribenoside + lidocaine (TL).

Study	Design	Total number of patients	Treatment	Main outcomes
Delarue ²⁴	Observational study	40 women with hemorrhoids as a consequence of pregnancy or delivery	All patients received oral tribenoside 400 mg 2-6 times daily for 10 days (post-partum) or 20 days (pregnancy). Local treatment with TL suppositories twice daily was administered for 5 days in 19 women who compelled bothersome pain	<ul style="list-style-type: none"> Efficacy rated as 'Excellent' in 15 patients. Fast relief from symptoms. No adverse events.
Vargas-Lozano ²⁵	Observational study	30	Tribenoside 400 mg + lidocaine 40 mg suppositories tid for 14 days	<ul style="list-style-type: none"> Treatment efficacy rated as "Excellent" in 11 and "Good" in 13 subjects, Excellent tolerability.
Da Silva ²⁶	Observational study	30	Oral tribenoside (200 mg tid) and local tribenoside 5% + lidocaine 2% cream bid, for 14 days	<ul style="list-style-type: none"> Anal itching disappeared in 75%, smarting in 72% and pain in 57% of cases.
Zurita-Briceno ²⁷	Observational study	30	Tribenoside 400 mg + lidocaine 40 mg suppositories tid for 28 days	<ul style="list-style-type: none"> 50% rated efficacy as 'Excellent'. No adverse events related to treatment.

taining only tribenoside^{20,21}. Tribenoside+lidocaine was compared with steroid-containing preparations in 6 studies^{17,19-23}. Last, two studies evaluated the efficacy and tolerability of the tribenoside+lidocaine combination in women with hemorrhoids as a consequence of pregnancy or delivery^{19,24}.

All the above-mentioned studies were well-conducted and can provide a comprehensive evaluation of tribenoside+lidocaine in the treatment of hemorrhoids. However, they were often local studies, published in languages other than English and, therefore, clinicians and researchers may not be immediately familiar with their results. Thus, a short summary of the key aspects of each study is reported here.

*Rizzi et al*¹⁷

Rizzi et al have published, in a single paper, the results of different analyses on the combination of tribenoside+lidocaine: (i) a double-blind study comparing tribenoside 5% + lidocaine 2% cream (n=14) with a semi-placebo cream (excipients + lidocaine 2%; n=14); (ii) an open-label investigation on tribenoside+lidocaine cream only (n=60); (iii) an open-label investigation on tribenoside+lidocaine suppositories (n=44); (iv) a comparison of the study combination with steroids-containing preparations (hydrocortisone or triamcinolone or fluocortolone or prednisolone (n=45). All tribenoside+lidocaine preparations were applied twice daily for up to ten days. A global assessment of treatment efficacy (good, medium, ineffective) was performed. Clinical evaluation of each objective (secretion, hemorrhage, nodules) and subjective (pain, burning, pruritus) symptoms was also carried out using a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe).

Results from the double-blind investigation (i) showed that the overall clinical efficacy was rated as "good" in 13 patients on tribenoside+lidocaine, compared with 4 patients on lidocaine only ($p<0.01$); (Figure 1) treatment was judged as "ineffective" in no patients on the combination treatment, versus 4 subjects in the other group ($p<0.01$). Both formulations of tribenoside+lidocaine resulted in a rapid symptom improvement, with effect on subjective symptoms being already evident before a maximum of 30 minutes since administration. Notably, a statistically-significant superiority ($p<0.001$) was also observed when evaluating the number of preferences in favor of tribenoside+lidocaine compared with those for steroid-containing preparations (Figure 2). Tolerability, both general and local, proved very good.

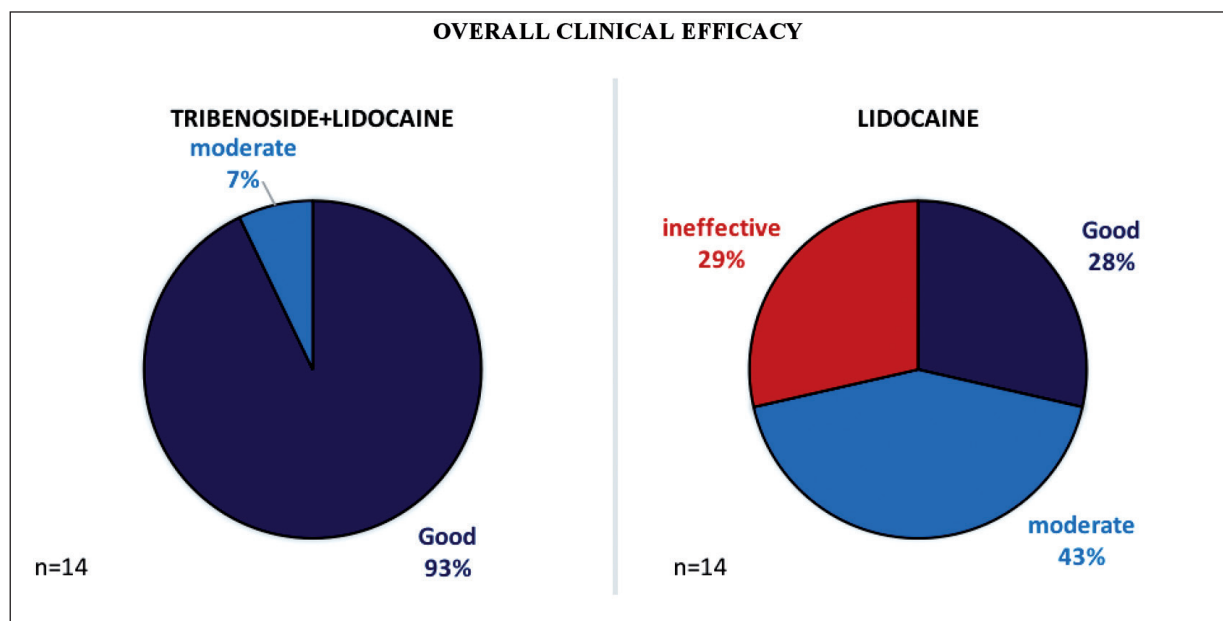


Figure 1. Results from the double-blind investigation (i) showing the proportion of cases in which the therapeutic effect of the combination or lidocaine semi-placebo was rated as “good”, “moderate” or “ineffective”. Differences between the two preparations were statistically significant ($p<0.01$)¹⁷.

*Fontana*¹⁸

A double-blind comparative study of tribenoside 5% and lidocaine 2% cream versus semi-placebo cream containing lidocaine only, using a scheme of sequential analysis, was performed

in 24 pairs of patients (34 males; mean age 49 years) suffering from hemorrhoids. Both preparations were applied for up to 10 days. Overall, tribenoside+lidocaine cream was significantly superior over semi-placebo in providing rapid relief

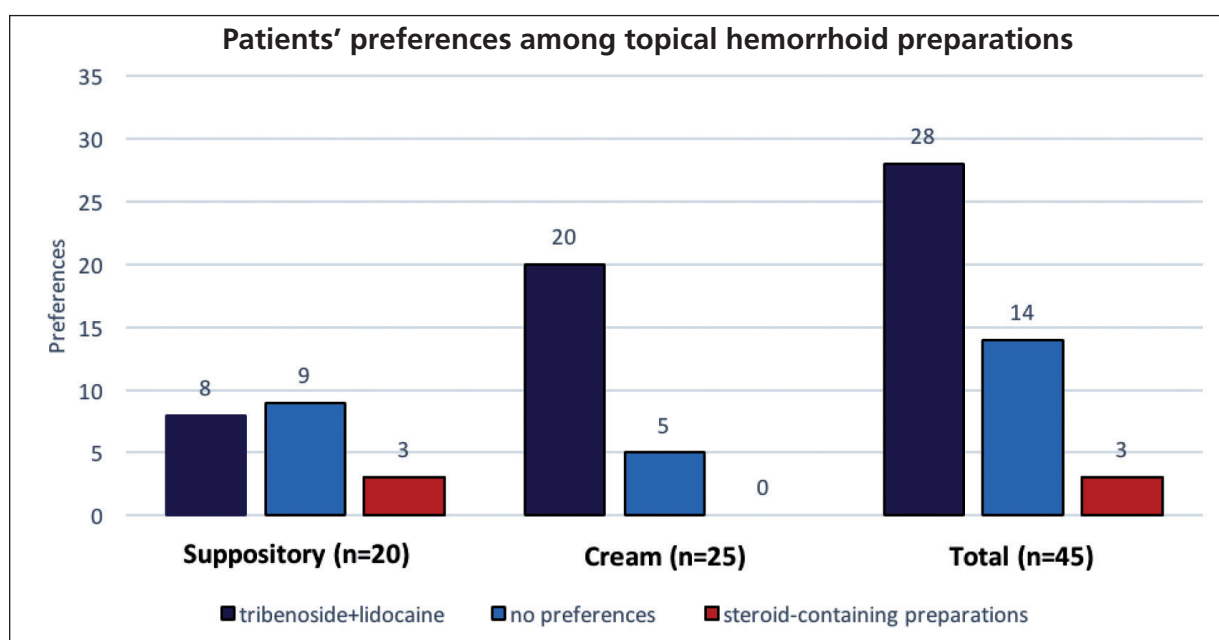


Figure 2. Patients’ preferences for tribenoside+lidocaine preparations (suppository and cream) or other standard care steroid-containing preparations¹⁷.

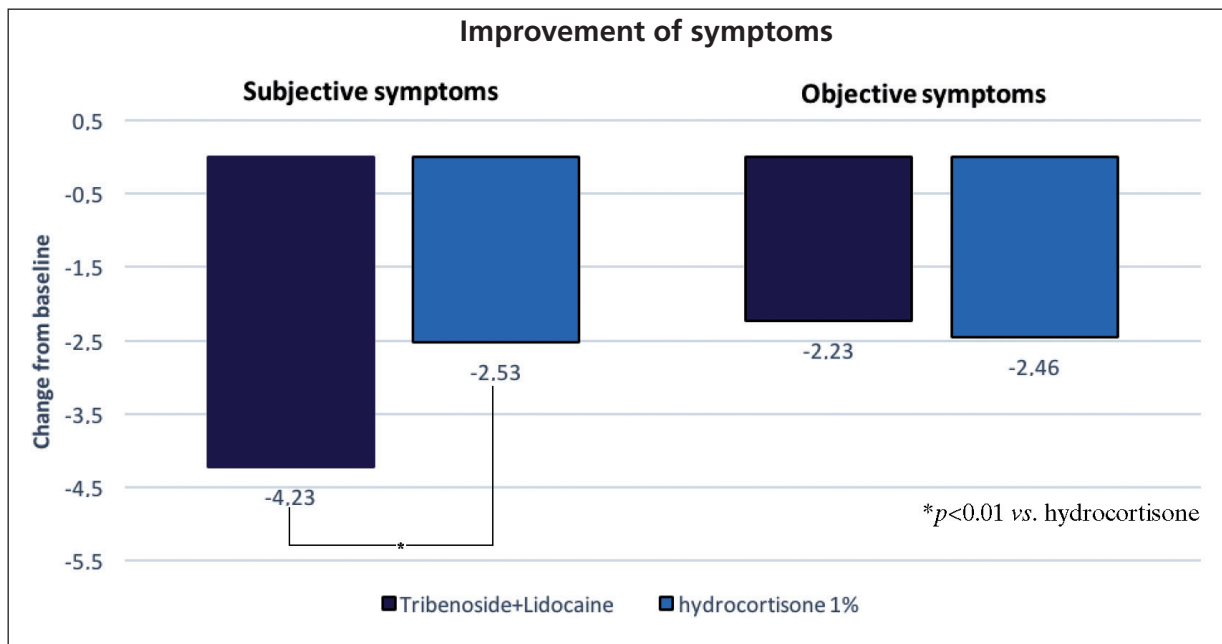


Figure 3. Improvement of subjective and objective symptoms of hemorrhoids with tribenoside + lidocaine and hydrocortisone containing preparation, expressed as difference in the score reported after treatment and the score reported at baseline. $p < 0.001$ for both preparations vs. baseline; $p < 0.01$ for tribenoside+lidocaine vs hydrocortisone 1% in the effect on subjective symptoms¹⁹.

on both subjective (pain, itching, sense of weight and tenesmus) and objective (inflammation, hemorrhage, secretion) symptoms of hemorrhoids ($p = 0.01$ vs. placebo). Local and general tolerability were excellent, no adverse reactions were observed in any of the 48 treated patients. Clinical efficacy was rated as “Very good” in 15 patients assigned to the study combination and 3 subjects on lidocaine only ($p = 0.01$).

Moggian¹⁹

In another randomized, double-blind study, tribenoside 400 mg + lidocaine 40 mg suppositories ($n = 21$), administered for up to 10 days’ treatment, were compared with a semi-placebo (excipient + lidocaine 40 mg only; $n = 20$); in a parallel double-blind evaluation, tribenoside+lidocaine suppositories ($n = 13$); all preparations were compared with hydrocortisone 1% suppositories ($n = 13$) all preparations in the study were administered b.i.d.. All patients were women (mean age, 33 years) suffering from hemorrhoids as a consequence of pregnancy or delivery. Both objective (secretion, hemorrhage, nodules) and subjective (pain, burning, itching) symptoms were assessed according to a 4-point scale for each symptom (0=absent, 1=mild; 2=moderate; 3=severe)..

Tribenoside+lidocaine suppositories significantly improved both subjective (mean score at

baseline: 4.62; mean score after treatment: 0.24; $p < 0.01$) and objective (2.86 vs. 0.91; $p < 0.01$) symptoms of hemorrhoids, likely because the presence of both lidocaine – with a fast action on subjective symptoms – and tribenoside – able to ameliorate objective symptoms and improve vascular tone. On the other hand, patients on lidocaine only experienced a relief of subjective symptoms (5.75 vs. 3.25; $p < 0.01$), but no effect on objective symptoms was reported (3.30 vs. 1.90).

The comparison with hydrocortisone preparation showed a significant effect on the subjective and objective symptomatology ($p < 0.001$). Notably, a significant difference in favor of tribenoside+lidocaine over steroid-containing preparations was observed in the improvement of subjective symptoms (tribenoside+lidocaine: -4.23 vs. baseline; steroids: -2.53 vs. baseline; $p < 0.01$) (Figure 3). The tolerability of tribenoside+lidocaine was judged as excellent.

Marques et al²⁰

This was a controlled, double-blind, multicenter investigation in which tribenoside+lidocaine, either as cream or suppositories, was compared with tribenoside alone, prednisolone trimethylacetate 0.1% + vioform 5% or fluocinolone acetonide 0.01% + bismuth gallate 5% + lidocaine 2% (all comparators were administered in

either cream or suppository formulation). In total, 462 patients of either gender were evaluated.

The results demonstrated the similar efficacy of the four preparations, as assessed using a 4-point scale. In particular, the Authors of this study recommended the use of tribenoside+lidocaine, thanks to its favorable safety profile and its rapid and effective action.

*Angriman and Neumayer*²¹

Angriman and Neumayer conducted a single-blind investigation on tribenoside+lidocaine cream (n=8), tribenoside 5% cream (n=8), prednisolone pivalate 0.1% + vioform 5% cream (n=8), and fluocinolone acetonide 0.01% + lidocaine 2% cream (n=16). All treatments were administered for up to 10 days. Overall, tribenoside+lidocaine cream showed an efficacy comparable with that of controls – as expressed in terms of subjective and objective symptoms improvement – and an excellent tolerability, since it did not share the side-effects reported with steroid-containing preparations.

*Berson et al*²²

In this double-blind investigation, tribenoside 400 mg + lidocaine 40 mg suppositories (n=147) were compared with prednisolone-containing suppositories (n=142). Patients (mean age: 43 years) were treated once daily for a maximum of 14 days. Symptoms improvement and global assessment of treatment effect were evaluated.

The excellent anti-phlogistic effect of the tribenoside+lidocaine combination was confirmed also in this study. The frequency of improvement of each symptom of hemorrhoids was similar in the two groups; however, a trend to an advantage in terms of nodules improvement was observed for tribenoside+lidocaine, compared with prednisolone (patients improved: 10/14, 71.4% vs. 7/21, 33.3%). The onset of action with tribenoside+lidocaine was also faster. The majority of both physicians and patients rated the efficacy of the tribenoside +lidocaine combination as “good” (59.7% and 62.5%, respectively).

*Holzer*²³

In this randomized, double-blind study, tribenoside+lidocaine suppositories (400/40 mg bid) or cream (5%/2% mg) was compared with an hydrocortisone-containing preparation, either in cream or suppository form. 53 patients (27 males) were treated for 21 days. In line with the above-mentioned studies, no statistical dif-

ferences were observed between the study combination and hydrocortisone treatment; however, the Author of this study stated that adverse events associated with corticoid-treatments could be avoided using tribenoside+lidocaine preparations.

*Delarue*²⁴

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 (post-partum) or 20 days (pregnancy). Local treatment with tribenoside+lidocaine suppositories twice daily was administered for 5 days in 19 women who compelled bothersome pain. Efficacy was rated as “Excellent” in 15 patients, “Good” in 18 and “Minimal” in 7 subjects, with positive results in 82.5% of cases, and a fast onset of symptom relief was reported, from 10 minutes since administration up to 10-12 hours. Tolerability was excellent in all patients: no systemic or local adverse effects were observed.

*Vargas Lozano*²⁵

In this study, 30 patients (14 men, mean age: 37 years) were treated with tribenoside+lidocaine suppositories tid for 2 weeks. Treatment efficacy was rated as “Excellent” in 11 and “Good” in 13 subjects, with 80% of patients, therefore, showing favorable results. In particular, most evident symptom improvements were observed for pain, bleeding, burning and pruritus. Tolerability was excellent in all cases.

*Da Silva*²⁶

30 patients with hemorrhoids received combined treatment with oral tribenoside (200 mg tid) and local tribenoside+lidocaine cream bid, for two weeks.

The treatment was “excellent” in the reduction of bleeding in 93% of cases. Anal itching disappeared in 75%, smarting in 72% and pain in 56% of cases, while considerable improvement in those symptoms occurred in 8%, 22% and 30%, respectively.

*Zurita-Briceno*²⁷

In this single-arm study, 30 patients (5 men, mean age: 46 years) were treated with tribenoside+lidocaine suppositories tid for 4 weeks. Efficacy was judged as “Excellent” in 15 (50%), “Good” in 10 (33%), “Moderate” in 4 (13%) and “Insufficient” in 1 (3.3%) patients. Only few ad-

verse events were reported, and all of them were considered poorly related to treatment.

Implications for Clinical Practice

Hemorrhoids are a widespread condition associated with a number of bothersome symptoms, either of subjective (e.g. pain, burning and itching) or objective (e.g. bleeding, swelling and nodules) nature.

At present, available medical treatments for low-grade hemorrhoids are supported by poor-quality evidence, and the pharmacological rationale behind at least some treatment is questionable¹. The standard treatment is represented by steroids; however, these molecules are burdened with a not-completely favorable toxicity profile also because of the risk of systemic adsorption, which may limit their application over the middle-term period or in some particular populations of patients such as pregnant/breastfeeding women (a population at high risk of developing hemorrhoids), elderly, patients with some infections (e.g. mycoses, HSV, local viral infections, TBC) or athletes.

The combination of tribenoside+lidocaine is a single formulation (cream or suppositories) containing two different molecules characterized by complementary actions. Tribenoside has the potential to ameliorate microcirculation, promote the healing of basement membrane and improve local microcirculation and vascular tone, thus improving the objective symptoms of hemorrhoids. On the other hand, lidocaine is a widely-used local anesthetic, able to induce a rapid relief of subjective symptoms such as local pain and discomfort which may be perceived as the most bothersome by patients.

Given its rapid comprehensive efficacy on all different symptoms of hemorrhoids, the tribenoside+lidocaine combination can find a place in the treatment of this condition. Importantly, its efficacy and safety have been formally evaluated in a number of well-conducted studies, mostly of which included a comparator arm using a reference treatment for the therapy of hemorrhoids. Overall, the combination of tribenoside and lidocaine was superior over the single components in symptoms improvement, likely thanks to its ability to ameliorate both subjective and objective symptoms at the same time. The effects on subjective symptoms were rapidly (10-30 minutes) observed after the administration of the combination. Moreover, in the reported studies, the treatment has been ef-

fectively used for up to 20 days without being associated with any relevant adverse event and showing an excellent tolerability. With respect to other preparations used in clinical practice, the tribenoside+lidocaine combination shows a long-lasting effect, likely due to the presence of the anti-inflammatory tribenoside. This long lasting-effect allows a twice daily administration until acute symptoms diminish, after which the dosage can be reduced to once a day¹³. The observed efficacy with this limited number of administrations/day is dependent upon the long-lasting pharmacological effect of the combination. In all available study, the combination of tribenoside+lidocaine was characterized by an excellent tolerability, with only negligible adverse events being reported.

The combination of tribenoside+lidocaine was at least equally effective as the gold standard treatment for hemorrhoids, i.e. steroid-based preparations, and sometimes superior in providing a prompt relief of the bothersome symptoms such as pain and itching. Since the use of steroids is not recommended for prolonged periods due to the possible steroid-related side-effects, tribenoside+lidocaine can represent. A fast, effective and safe option to treat hemorrhoids. Noteworthy, 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 pregnant women after the first trimester of pregnancy (although no randomized studies have been conducted in this specific population) and during breastfeeding. Also, the combination of tribenoside+lidocaine can be suitable for athletes or patients carrying some types of infections, in whom steroids cannot be administered.

Of note, the efficacy and safety of tribenoside+lidocaine were consistent regardless of the specific formulation and dosing regimen, and were also observed in women with hemorrhoids due to recent delivery or pregnancy. It is worth notice that the dosage of the combination was optimized for the specific formulations (cream or suppository) during the development phase of the product.

It must be acknowledged that all the studies evaluating tribenoside+lidocaine were conducted in the '70s of the last century. However, the design of these trials was robust, and the total number of evaluated patients exceed 1,000.

Conclusions

We believe that enough evidence exists to recommend the use of this combination therapy as a fast, effective and safe option for the local treatment of low-grade hemorrhoids.

Acknowledgement

Editorial assistance for the preparation of this manuscript was provided by Luca Giacomelli, PhD, on behalf of Content Ed Net; this assistance was funded by Recordati.

Conflicts of interest

The authors declare no conflicts of interest.

References

- 1) ALTOMARE DF, GIANNINI I. Pharmacological treatment of hemorrhoids: a narrative review. *Expert Opin Pharmacother* 2013; 14: 2343-2349.
- 2) JOHANSON JF, SONNENBERG A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. *Gastroenterology* 1990; 98: 380-386.
- 3) GANZ RA. The evaluation and treatment of hemorrhoids: a guide for the gastroenterologist. *Clin Gastroenterol Hepatol* 2013; 11: 593-603.
- 4) ABRAMOWITZ L, SOBHANI I, BENIFLA JL, VUAGNAT A, DARAI E, MIGNON M, MADELENAT P. Anal fissure and thrombosed external hemorrhoids before and after delivery. *Dis Colon Rectum* 2002; 45: 650-655.
- 5) QUIJANO CE, ABALOS E. Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. *Cochrane Database Syst Rev* 2005: CD004077.
- 6) STAROSELSKY A, NAVA-OCAMPO AA, VOHRA S, KOREN G. Hemorrhoids in pregnancy. *Can Fam Physician* 2008; 54: 189-190.
- 7) LOHSIRIWAT V. Treatment of hemorrhoids: A colorectalologist's view. *World J Gastroenterol* 2015; 21: 9245-9252.
- 8) 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.
- 9) MOUNSEY AL, HALLADAY J, SADIO TS. Hemorrhoids. *Am Fam Physician* 2011; 84: 204-210.
- 10) GOLIGHER JC. *Surgery of the anus, rectum and colon*. Balliere Tindal, London, 1980; pp. 93-135.
- 11) ALONSO-COELLO P, MILLS E, HEELS-ANSELL D, LÓPEZ-YAR-TO M, ZHOU Q, JOHANSON JF, GUYATT G. Fiber for the treatment of hemorrhoids complications: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 181-188.
- 12) MOESGAARD F, NIELSEN ML, HANSEN JB, KNUDSEN JT. High fiber diet reduces bleeding and pain in patients with hemorrhoids: a double blind trial of Vi-Siblin. *Dis Colon Rectum* 1982; 25: 454-456.
- 13) Procto-Glyvenol SPC.
- 14) KIKKAWA Y, TAKAKI S, MATSUDA Y, OKABE K, TANIGUCHI M, OOMACHI K, SAMEJIMA T, KATAGIRI F, HOZUMI K, NOMIZU M. The influence of Tribenoside on expression and deposition of epidermal laminins in HaCaT cells. *Biol Pharm Bull* 2010; 33: 307-310.
- 15) JAQUES R. The pharmacological activity of tribenoside. *Pharmacology* 1977; 15: 445-460.
- 16) BARKIN RL. The pharmacology of topical analgesics. *Postgrad Med* 2013; 125(4 Suppl 1): 7-18.
- 17) RIZZI B, GIACOMINI F, BANDINI V. Terapia locale della sindrome emorroidaria con etil-3,5,6-tri-o-benzil-d-glicofuranoside: risultati clinici. *Gazz Int Med Chirur* 1972; 77: 1598-1606.
- 18) FONTANA G. Trattamento della sindrome emorroidaria con un derivato glicofuranosidico in crema associato ad un anestetico. *Gazz Med Ital* 1973; 132: 32-35.
- 19) MOGGIAN G. Sperimentazione clinica controllata di un derivato glicofuranosidico anti-emorroidario, per uso locale. *Minerva Med* 1973; 64: 215-218.
- 20) MARQUES JR, DA SILVA JH, GALIZIA I, KERZNER A, NETTO GM, MOREIRA GO, DA CRUZ GMG, ZERBINI JC, D'ARAÚJO MA, SIMONSEN OS, JATOPA PP, DE SOUZA CE.. Ensaio controlado com Procto-Glyvenol no tratamento das hemorroides. *Rev Bras De Cirurgia* 1972; 62: 7-8.
- 21) ANGRIMAN J, NEUMAYER F. Tratamiento de las hemorroides con glucofuranosido crema. *Orientación Médica* 1972; 31: 353-354.
- 22) BERSON I, GEISER JD. Utilisation d'un nouveau produit: le procto-glyvenol en pratique proctologique. *Revue Suisse de Médecine (Praxis)* 1975; 63: 19-22.
- 23) HOLZER A. Betrachtungen über ano-rektale leidenszustände und ihre behandlung. *Der Praktische Arzt* 1976; 30: 662-672.
- 24) DELARUE T. Traitement de la maladie hemorroïdaire pendant la grossesse et le post partum par le glyvenol. *Arch Med Ouest* 1977; 9: 637-641.
- 25) VARGAS LOZANO R. Tratamiento sintomático en hemorroides con glucofuranosidos topicos. *Medicina (Rev. Mex.)* 1972; 52: 575-578.
- 26) DA SILVA A. Doença hemorroidaria – tratamento clinico com o tribenosido. *Folha Méd* 1976; 73: 531-536.
- 27) ZURITA-BRICENO L. Tratamiento topico de hemorroides con glucofuranosido. *Medicina (Rev. Mex.)* 1972; 52: 229-232.