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Troxerutin–Carbazochrome Combination Versus Placebo in the Treatment of Posthemorrhoidectomy Symptoms: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: Flavonoids, such as troxerutin, have been shown to be safe and effective agents for the treatment of chronic venous insufficiency. The fixed combination of troxerutin 150 mg plus carbazochrome (an oxidation product of epinephrine that enhances the microcirculatory tone) 1.5 mg has been shown to have a good efficacy and tolerability profile in nonsurgical patients with acute, uncomplicated hemorrhoids. A previous pilot study we carried out in 30 posthemorrhoidectomy patients showed that this combination was also effective and well tolerated in improving posthemorrhoidectomy symptoms.

Objective: This study compared the efficacy and tolerability of troxerutin–carbazochrome active combination with placebo in the treatment of posthemorrhoidectomy symptoms.

Methods: In this single-center, randomized, double-blind, placebo-controlled study, patients scheduled for hemorrhoidectomy were randomized to receive 1 of 2 treatments: troxerutin 150 mg plus carbazochrome 1.5 mg active combination or placebo IM in 3-mL ampules BID for 5 consecutive days after surgery, starting on the day of surgery. Efficacy parameters were assessed at baseline (T1), after the first administration (T2; day of surgery), day 2 after surgery (T3), and day 5 after surgery (T4). Efficacy parameters assessed included hemorrhoidal symptoms based on a visual analog scale (VAS): pain, discharge, bleeding, inflammation, and pruritus; edema; analgesic intake, if any; time to restore physiologic defecation; photographs taken at T1 and T4 (in selected patients; not included here); and standard blood coagulation tests.

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Results: Sixty patients were enrolled (33 males, 27 females; mean age, 45.6 ± 7.4 years). Analysis between treatment groups revealed significant differences in mean total VAS scores at T3 and T4 ($P = 0.01$ and $P = 0.001$, respectively) in favor of the active-combination group. Statistically significant between-group differences in scores for bleeding and pruritus at T3 and for bleeding, pruritus, and edema at T4 in favor of the active-combination group also were found ($P < 0.001$ for all). No severe adverse events were reported in either group. Blood coagulation test results were unaffected in both groups.

Conclusions: IM administration of troxerutin 150 mg plus carbazochrome 1.5 mg combination was effective, well tolerated, and superior to placebo in improving hemorrhoidal and postsurgical signs and symptoms in 5 days of treatment in this study population.

Key words: flavonoids, troxerutin, carbazochrome, hemorrhoid. (*Curr Ther Res Clin Exp.* 2002;63:527–535)

INTRODUCTION

Hemorrhoids are one of the most common afflictions in the Western world. They can occur at any age and can affect both women and men. Because the presence of hemorrhoidal tissue is normal—it acts as a compressible lining that allows the anus to close completely—disease should be thought of as hemorrhoidal tissue that causes significant symptoms. Unfortunately, hemorrhoids tend to worsen over time, and the disease should be treated as soon as it occurs.

The best treatment is prevention. A diet high in fiber and bulk can prevent constipation, reducing the risk for hemorrhoids.[1] If the diet cannot be modified in this way, adding bulk laxatives may be necessary and can prevent worsening of constipation. Numerous creams and suppositories can relieve the anal irritation and pain of hemorrhoids, but they rarely provide any long-term benefit.

For patients who have grade I or II hemorrhoids or who have larger hemorrhoids but wish to avoid surgical treatment, outpatient procedures (eg, sclerotherapy, photocoagulation, rubber band ligation, cryotherapy) may be appropriate. If symptoms recur after topical treatment, the patient can be treated with an additional application or a different topical treatment, or hemorrhoidectomy may be considered for more definitive control of symptoms. Hemorrhoidectomy is necessary when clots repeatedly form in external hemorrhoids, ligation fails to treat internal hemorrhoids, the protruding hemorrhoid cannot be reduced, or persistent bleeding occurs.[2]

Venous insufficiency can be treated with venotonic agents. These drugs improve the structure of local capillary vessels, which are most affected by dilation and local venous insufficiency. The effects of such drugs on capillary structure (ie, improving its permeability and resistance as well as its reactivity to endogenous amines), their anti-inflammatory action in the local lymphatic

system[3] (thereby reducing local edema), their inhibitory activity on the generation of reactive oxygen radicals,[4] and their ability to reduce blood viscosity[5] make them useful agents in the treatment of hemorrhoidal episodes.

A qualitative data aggregation[6] carried out to assess the therapeutic effect of venotonics in chronic venous insufficiency (CVI) concluded that the administration of these drugs can reduce symptoms in these patients; decreases in limb circumference and venous capacity and an increase in venous outflow also were found.

Flavonoids, such as troxerutin, have been shown to be safe and effective agents for the treatment of CVI.[7,8] Troxerutin (2-[3,4-bis{2-hydroxyethoxy} phenyl]-[[6-*O*-deoxy-alpha-L-manno-pyranosyl-beta-D-glucopyranosyl]-oxy]-5-hydroxy-7-(2-hydroxyethoxy)-4H-1-benzo-pyran-4-one) is the main component of a mixture, the *O*-(beta-hydroxyethyl) rutosides, which also contain mono-, di-, tetra-, and other trihydroxyethyl derivatives of rutosides. The term *oxerutins* is applied to a mixture of 5 different *O*-(beta-hydroxyethyl) rutosides, not less than 45% of which is troxerutin. Troxerutin shows a marked affinity for the venous wall. The highest uptake in the outer wall region is likely to result from transport through the vasa vasorum due to the rheologic properties of the drug.[9] Troxerutin significantly inhibits platelet adhesion to the extracellular matrix, yields an antierythrocyte aggregation effect, and exerts a favorable action on the blood fibrinolytic system.[10] Parenteral troxerutin* 150 mg is currently licensed in Italy in combination with carbazochrome, an oxidation product of epinephrine that enhances the microcirculatory tone. This product is widely used for the relief of acute hemorrhoidal episodes.

We have previously shown that the fixed combination of these 2 active substances also had a good efficacy and tolerability profile in the treatment of 30 posthemorrhoidectomy patients.[11] Because this was a pilot investigation carried out to assess the efficacy of this use in postsurgical patients, the purpose of this single-center, randomized, double-blind, placebo-controlled study was to further investigate the efficacy and tolerability of this therapeutic regimen in the posthemorrhoidectomy period on a new and larger patient population.

PATIENTS AND METHODS

Patients

Patients aged 18 to 65 years presented at the Surgery Unit and Colon Proctology Unit, University of Chieti-Pescara, Pescara Regional Hospital, Pescara, Italy, for hemorrhoidectomy or rubber band ligation. Indications for these procedures included pain, bleeding, discharge, edema, inflammation, or thrombosis that, when assessed using physical examination (rectoscopy) showed the presence of hemorrhoids considered responsible for the patients' symptoms.

*Trademark: Fleboside® (Acarpia Lda., Madeira, Portugal).

Patients with chronic or severe disease (eg, diabetes mellitus, coagulation disorders, oncologic conditions), altered hepatic or renal function, pelvic tumor, or portal hypertension were excluded. Other reasons for exclusion were unwillingness to cooperate, poor motivation, or other emotional or intellectual problems likely to either invalidate the informed consent or limit the ability to comply with protocol requirements; participation in other studies involving investigational or marketed products within 1 month preceding study entry, or concomitant with the study; a history of allergy or hypersensitivity to troxerutin and/or carbazochrome; pregnancy; and lactation.

The study was approved by the center's institutional review board and was conducted according to International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent before entering the study.

Patients were not allowed to take any local or systemic treatment for their hemorrhoidal condition for >24 hours within 5 days of study initiation, except for a standardized analgesic drug (ketorolac 30-mg tablets). The consumption of the analgesic was recorded and considered a part of the efficacy assessment.

Study Design

Using a central number table, patients were randomized to receive 1 of 2 treatments: troxerutin 150 mg plus carbazochrome 1.5 mg active combination or placebo IM in 3-mL ampules BID for 5 consecutive days after surgery, starting on the day of surgery. Thus, every patient received 6 mL/d. Active combination and placebo were packaged in an identical manner, and the IM injection was performed by a licensed nurse rather than the responsible physician to maintain the double-blind condition because the color of the active solution was different from that of the placebo. The fact that the nurse was not blinded could not have led to bias in request for pain medication or reporting of symptoms because he or she was unaware of the medications being given.

Physical examination and measurements of sitting systolic and diastolic blood pressure and heart rate were performed at baseline (T1) and day 5 after surgery (T4). Data were extrapolated from standard daily physical examinations and measurements.

Efficacy parameters were assessed at T1, after the first administration (T2; day of surgery), day 2 after surgery (T3), and T4. Efficacy parameters assessed included hemorrhoidal symptoms (pain, discharge, bleeding, inflammation, and pruritus, based on a 100-mm visual analog scale [VAS]) and edema (based on a 4-point categorical scale [0 = absent; 1 = mild; 2 = moderate; 3 = severe], extrapolated from standard daily examinations by an independent physician blinded on review of these data). For the symptoms assessed using the VAS, each was assessed separately; then the sum of scores was expressed on a single-patient VAS. The obtained VAS score was directly proportional to the intensity of symptoms (ie, the higher the number, the greater the intensity). Other efficacy parameters assessed included pain medication intake, if any;

time to restore physiologic defecation; photographs taken at T1 and T4 (in 15 selected patients [the selection was determined randomly and the photographic assessment took place in a blinded fashion]; not included here); blood coagulation tests (prothrombin time and partial thromboplastin time); relapses of symptoms; patient perception of efficacy (good, moderate, or poor); incidence of adverse events (AEs); compliance with treatment using direct patient interviews and nurse reporting; tolerability using laboratory tests (ie, blood chemistry and urinalysis) performed at T1 and T4; and the occurrence of new hemorrhoidal episodes using a standard follow-up visit 1 month after surgery.

Statistical Analysis

Age, body weight, height, vital signs, blood coagulation tests, and number of administered ketorolac tablets in the 2 groups were compared using the Student *t* test. Sex distribution, medical history, stool consistency, number of previous hemorrhoidal episodes, and patient perception of efficacy were analyzed using the chi-square test. Hemorrhoidal symptoms were analyzed using the Wilcoxon matched-pairs signed rank test for within-group differences and the Mann-Whitney *U* test for between-group differences.

The study was powered to detect a 10% within-group difference for the assessed population, taking into account the variance for the most important parameters—hemorrhoidal symptoms, especially pain, bleeding, and edema. Because such a small difference in subjective complaints may not have clinical significance and because the minimal clinically significant difference on a patient's VAS has been shown to be ~7 to 11 mm,[12] a sum of each individual's VAS scores also was calculated to provide a more reliable and clinically meaningful assessment. Accepted error levels were alpha = 0.05 and beta = 0.10. Statistical significance was set at $P \leq 0.05$.

RESULTS

Eighty-five patients were screened for entry into the study during a 1-year period. Seven patients had insufficient data on the case-report form, 9 did not give informed consent at the baseline visit, 6 were taking an analgesic other than ketorolac at baseline, 1 was given micronized flavonoid fraction of diosmin immediately before surgery, and 2 had portal hypertension. The remaining 60 patients (33 males, 27 females; mean age, 45.6 ± 7.4 years) were enrolled. Twenty-nine patients (48.3%) received the active combination, and 31 (51.7%) received placebo.

At baseline, both the active-combination and placebo groups were comparable with respect to sex distribution, mean age (46.5 ± 8.9 years vs 43.1 ± 10.8 years), mean body weight (79.2 ± 11.9 kg vs 77.6 ± 12.7 kg), mean height (164.2 ± 3.8 cm vs 159.5 ± 5.1 cm), time since last episode, medical history, and stool consistency.

Table I. Mean 100-mm visual analog scale (VAS) and 4-point edema scores at baseline (T1) and at 1 day (T2), 2 days (T3), and 5 days (T4) of treatment with troxerutin–carbazochrome active combination versus placebo after surgery.

	Active Combination (n = 29)				Placebo (n = 31)			
Symptom*	T1	T2	T3	T4	T1	T2	T3	T4
VAS†								
Pain	0.12	0.10	0.90	0.45	0.11	0.10	0.90	1.10‡
Bleeding	0.40	0.50	0.40§	0.30§	0.50	0.80	2.00	1.00‡
Inflammation	0.10	0.15	0.50	0.10	0.09	0.12	1.00	0.50
Pruritus	0.01	0.10	0.50§	0.10§	0.02	0.12	1.37	1.30‡
Total	0.63	0.85	2.30‖¶	0.70#	0.72	1.14	5.77‡	3.90
Edema	0.65	0.62	0.90**	0.42§	0.74	0.74	1.65¶	1.15‡

*Discharge measurements did not change and so are not shown.
†Data are shown in centimeters.
‡$P < 0.01$ versus baseline.
§$P < 0.001$ versus placebo.
‖$P = 0.01$ versus placebo.
¶$P < 0.05$ versus baseline.
#$P = 0.001$ versus placebo.
**$P = 0.05$ versus placebo.

Efficacy

Mean VAS and edema scores are shown in Table I. No significant between-group differences were found in baseline mean VAS scores and analgesic consumption. Based on physical examination and medical history, a family history of venous insufficiency, many hours spent in the standing or sitting position, and hard consistency of stools were common in both groups. Eighteen of 29 (62.1%) patients in the active-combination group and 20 of 31 (64.5%) patients in the placebo group reported hard stools at baseline.

Analysis of differences between treatment groups revealed a significant difference in mean total VAS scores at T3 and T4 in favor of the active-combination group ($P = 0.01$ and $P = 0.001$, respectively). An analysis of scores for individual symptoms revealed significant between-group differences in scores for bleeding and pruritus at T3 and for bleeding, pruritus, and edema at T4 ($P < 0.001$ for all) in favor of the active-combination group. The between-group difference in edema scores at T3 was statistically significant, although not clinically relevant, in favor of the active-combination group ($P = 0.05$).

The natural course of hemorrhoidal symptoms after surgical therapy is illustrated by the results observed in the placebo group. The scores in assessed symptoms peaked at T3 ($P < 0.01$ for mean total VAS score vs baseline mean total VAS score; $P < 0.05$ for mean edema score vs baseline mean edema score). At T4, significant within-group differences were found in mean scores for pain, bleeding, pruritus, and edema versus these scores at baseline ($P < 0.01$ for all).

In the active-combination group, the scores in all assessed symptoms also peaked at T3 but were clinically less severe ($P < 0.05$ for mean total VAS score vs baseline; nonsignificant for mean edema score vs baseline). At T4, no significant difference was found in any mean symptom scores compared with baseline.

Consumption of analgesic peaked at T3. Analgesic intake was comparably low in both groups (7 [24.1%] patients in the active-combination group, 9 [29.0%] patients in the placebo group), with no significant difference between groups.

No patients developed new hemorrhoidal episodes during the treatment period, and no episodes were reported at the follow-up visit 1 month after surgery. Physiologic defecation was restored at T3 in all patients except for 1 patient in the placebo group.

Adverse Events

No severe AEs were reported in either group. Two mild and self-limiting AEs (cephalgia and erythema at the injection site) were reported in the active-combination group, and 3 (vertigo, cephalgia, and pain at the injection site) were reported in the placebo group. No dropouts due to AEs occurred.

Laboratory Tests

Blood coagulation test results were unaffected in both groups (Table II). No statistically or clinically significant within-group differences in laboratory test results (ie, blood chemistry and urinalysis) were found between T1 and T4 (data not shown) in either group.

DISCUSSION

Flavonoids are a class of naturally occurring compounds with excellent free radical–scavenging properties.[4] Flavonoids reduce the decrease in adenosine

Table II. Blood coagulation test results at baseline (T1) and at 5 days (T4) of treatment with troxerutin–carbazochrome active combination versus placebo after surgery. Values are expressed as mean ± SD.*

	T1		T4	
Test	Active Combination (n = 29)	Placebo (n = 31)	Active Combination (n = 29)	Placebo (n = 31)
PT, %	104.6 ± 17.5	107.1 ± 14.2	103.5 ± 16.3	106.9 ± 15.8
PTT, s	32.5 ± 6.4	33.9 ± 3.8	33.1 ± 5.7	33.7 ± 2.5

PT = prothrombin time; PTT = partial thromboplastin time.
*None of the within-group or between-group differences were statistically significant.

triphosphate in venous endothelial cells during hypoxia. This decrease attenuates (1) the inflammatory response, (2) the adherence of neutrophils,[13] (3) damage to the veins, and (4) the release of growth factors. Such properties have been exploited in the management of CVI[7] and chronic doxorubicin-induced cardiotoxicity.[14]

Because hemorrhoids are a result of CVI, flavonoids, alone or in combination with other drugs, have been used widely in patients before treatment with more aggressive procedures, such as sclerotherapy or surgery.[7,8]

The troxerutin–carbazochrome active combination has been shown to be effective and tolerable in nonsurgical patients when administered parenterally at the same doses used in the present study.[15] In a previous, smaller-scale investigation in 30 patients,[11] we found that this drug regimen could be used effectively in the postsurgical period to attenuate signs and symptoms after hemorrhoidectomy or rubber band ligation.

The results of the present study confirm our previous findings, but in a larger population of patients, and are consistent with those from other studies in the treatment of hemorrhoidal episodes.[7,8,13] Edema, inflammation, pruritus, and bleeding were notably improved in the active-combination group compared with the placebo group.

A 5-day treatment period was sufficient to achieve significant resolution of hemorrhoidal symptoms assessed. Treatment with the active combination was well tolerated, and compliance was >95% in this set of hospitalized patients. These results suggest that the troxerutin–carbazochrome combination has significant effects on the quality of life and health care costs in this patient population.

CONCLUSIONS

IM administration of the active combination of troxerutin 150 mg plus carbazochrome 1.5 mg was effective, well tolerated, and superior to placebo in improving hemorrhoidal symptoms in 5 days of treatment in this study population.

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