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Double-blind, randomized clinical trial of troxerutin-carbazochrome in patients with hemorrhoids

F. SQUADRITO, D. ALTAVILLA, S. OLIARO BOSSO*

Istituto di Farmacologia, Servizio di Farmacologia Clinica, University of Messina (Italy)
**Pharmafar Srl – Torino (Italy)*

Abstract. – **This multicenter, double-blind, randomised study was undertaken to determine the efficacy and safety of a combination of troxerutin 150 mg and carbazochrome 1.5 mg compared to carbazochrome alone in patients with acute uncomplicated hemorrhoids.**

Patients were administered by the intramuscular route (one ampoule) twice daily for one week.

Both subjective and objective efficacy variables significantly improved in the combination drug group only, thus demonstrating the rationale for a combination therapy.

Treatments were safe and well tolerated either at a local or systemic level.

Key Words:

Troxerutin, Carbazochrome, Hemorrhoids, Controlled clinical trial.

Introduction

The combination of troxerutin and carbazochrome (Fleboside® ampoules) finds its rationale on the pharmacological interaction of the two active components on the microcirculation.

Troxerutin – (2-[3,4-Bis(2-hydroxyethoxy) phenyl]-[[6-O-deoxy-a-L-mannopyranosyl)-β-D-glucopyranosyl]-oxy]-5-hydroxy-7-(2-hydroxyethoxy)-4H-1-benzopyran-4-one) – is a bioflavonoid and the main component of a mixture, the O-(β-hydroxyethyl) rutosides, which also contains mono-, di-, tetra-, and other trihydroxyethyl derivatives of rutin. The term oxerutins is applied to a mixture of 5 different *o*-(β-hydroxyethyl) rutosides, not less than 45% of which is troxerutin. This substance shows an ability to increase vascular resistance at the arteriolar level and to improve capillary function by reducing abnormal leakage. This compound is able to inhibit the enzyme cathechol-ortho-methyl-transferase (COMT); this, in turn, leads to more sustained local epinephrine levels. Other mechanisms of action have been claimed, involving an inhibition of jaluronidase and histamine synthesis at the vascular wall, and a decreased blood viscosity and erythrocytes aggregation[1]. The profibrinolytic and rheological activities of troxerutin appeared well correlated with its plasma levels[2].

Carbazochrome – (3-hydroxy-1-methyl-1,5,6-indolinedione semicarbazone) – a stable oxy epinephrine derivative, devoid of any adrenergic action, is able to enhance microcirculatory tone, thus decreasing the hemorrhage time[3].

In patients with chronic venous insufficiency, this combination demonstrated to effectively control signs and symptoms of venous stasis with a twice-daily im administration and to be safe and well tolerated[4,5].

The primary objective of the present double-blind, randomised, controlled study was to evaluate efficacy and tolerability of this combination treatment regimen compared to carbazochrome alone, in patients with acute, uncomplicated hemorrhoids, in order to validate the rationale of the fixed combination product with relevance to the treatment of hemorrhoids.

Patients and Methods

Study design

This double-blind, parallel-group, controlled study was conducted on an out-patient population addressing to the Clinical Pharmacology Unit of the University of Messina.

Patient eligibility was determined at a screening visit at which a medical history was taken and a complete physical examination, including endoscopy, was performed.

Eligible patients (those meeting a diagnosis of acute uncomplicated hemorrhoids according to the Merck Manual[6]) were randomised to either receive the combination product (troxerutin 150 mg and carbazochrome 1.5 mg) twice daily by the intramuscular route, or one of the ingredients (saline containing carbazochrome 1.5 mg to give the solution the same appearance as the combination product) twice daily by the same route, during a 7-day period.

This study was performed in accordance with the requirements of ICH Good Clinical Practice, the Declaration of Helsinki as amended in Hong Kong in 1989, and institutional review board approval. The protocol and statement of informed consent were approved by the Institutional Review Board prior to the beginning of the trial. Written informed consent was obtained from each patient before entry the study, and patients were informed of their right to withdraw at any time.

Patients

Patients with acute uncomplicated hemorrhoids who were at least 30 years of age were eligible if their diagnosis was endoscopically confirmed. All patients who entered the double-blind treatment period were required to have developed hemorrhoidal symptoms during the preceding ten days in the absence of any other medication.

Patients with any of the following criteria were ineligible: advanced hemorrhoids requiring surgery; type I diabetes mellitus; congestive heart failure being treated with anti-platelet drugs; or presence of clinically significant renal, hepatic, or other concurrent severe disease. Use of fibrinolytic drugs, other venous-acting medications or an investigational drug within 30 days of screening, analgesic (other than a 5% lidocaine ointment) or non-steroidal anti-inflammatory drugs within 7 days of screening, or concomitant use of medications known to affect pain or hemostasis were not allowed. Women who were pregnant or lactating were excluded, as were patients with active alcohol or drugs abuse.

A total of 100 subjects were enrolled at the end of the screening period. Patients were the divided into two parallel groups of 50 subjects each, after the randomisation procedure.

Measurements

Clinical visits were scheduled weekly during the enrolment period, at the start of treatment, and after the 1-week period of treatment; a follow-up visit was scheduled 1 week after study completion.

Vital signs were measured and an interim medical history was taken at each clinic visit.

Vital signs were measured 3 times at 2-minute intervals after the patient sat quietly for at least 5 minutes, with mean sitting systolic blood pressure (sSBP), sitting diastolic blood pressure (sDBP), and sitting heart rate (SHR) calculated from the average of the 3 measurements.

Haematology, blood chemistry (including prothrombine time) and urinalysis were measured at screening and after the 1-week treatment period.

Efficacy variables

Subjective efficacy variables (anal discomfort, spontaneous local pain and pain at defecation), and objective signs (proctorrhagia, proctitis, anal prolapse), were evaluated by a four-point scale from 0 = absent to 4 = severe.

Safety assessment

All adverse events were coded from the verbatim term according to the World Health Organisation Adverse Reaction Terminology dictionary by body system and preferred term[6].

Vital sign measurements of concern were defined as follows:

SBP (< 120 mm Hg), DBP (< 60 mm Hg), and HR (< 50 o > 120 beats/min).

Statistical analysis

An intent-to-treat analysis of all patients randomly allocated to receive study medication or control drug was performed. Randomisation was performed using a pseudo-random number table generated by a validated software (GraphPad™, Sorrento Valley, California, USA).

The power of the study was assessed according to the following calculation:

Sample sizes were calculated using GraphPad StatMate version 1.01i, GraphPad Software, San Diego California USA, www.graphpad.com

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N per group	Power 99%	Power 95%	Power 90%
40	0.49	0.41	0.37
50	0.43	0.36	0.33

Anticipated SD of each group (assume equal): 0.5, Alpha = 0.05, two-tailed.

Clinical scores were analysed using a Wilcoxon pairwise statistics for each treatment group. Statistical significance between groups was determined using the two-tailed Mann-Whitney U test. For the safety assessments, summary statistics of laboratory test values and incidence of adverse events were determined.

Results

Patients

The groups of patients randomly allocated to receive study medication, or control drug had similar demographic and clinical characteristics at baseline (Table I).

All patients who were randomised were < 60 years of age and were Caucasian. The two study groups had a similar proportion of male and female patients.

Efficacy assessment

All symptom scores significantly decreased in the combination drug-treated patients ($p < 0.001$), whereas in the control group only anal discomfort and spontaneous pain showed a significant improvement ($p = 0.05$) (Figure 1).

Objective signs (proctorrhage, proctitis and anal prolapse) were not altered by the 7-day course of the control drug, but showed some amelioration after the study drug, with a significant reduction of local hemorrhage ($p < 0.001$) and inflammation ($p < 0.0001$).

The frequency of application of the local anaesthetic ointment significantly decreased ($p < 0.01$) in the active drug-treatment group only.

The results of the subgroup analysis of efficacy according to patients' age and sex were consistent with the analysis of the total patient population. However, the limited number of patients in each subgroup precluded statistical evaluation of differences between subgroups.

Table I. Patient demographics and clinical charateristics (means ± SD).

Characteristics	Controls (n = 50)	Study medication (n = 50)
Age	40.3 ± 8.2	40.6 ± 7.1
Sex, n (%)		
Female	21 (42%)	21 (42%)
Male	29 (58%)	29 (58%)
Body weight (kg)	70.8 ± 13.2	70.8 ± 17.1
Height (cm)	166.3 ± 7.7	166.3 ± 7.4
sSBP	128.90 ± 9.65	132.90 ± 12.33
sDBP	80.90 ± 4.91	82.90 ± 5.98
sHR	75.32 ± 4.74	6.09

sDBP = sitting diastolic blood pressure; sSBP = sitting systolic blood pressure; sHR = sitting heart rate.

Safety results

All subjects completed the study without experiencing any adverse reactions, both at the local and systemic level.

The mean changes from baseline in laboratory variables were generally small and less than 5% for each treatment group.

The exception was VES which decreased 8% in the combination drug group, this being possibly related to an anti-inflammatory activity secondary to an improvement of capillary function.

None of the patients had vital signs of clinical concern during the treatment period.

Discussion

Most hemorrhoids respond to conservative therapy such as suppositories, stool softeners or drugs acting at a microcirculatory level.

Troxerutin 150 mg + carbazochrome 1.5 mg Fleboside, is a commonly prescribed medicinal product in both the hospital and the out-patients settings.

When treated by the intramuscular route with the combination drug patients with acute uncomplicated hemorrhoids experienced a significantly higher improvement of subjective symptoms and objective signs of disease than those in the control group. The consumption of local anaesthetic was also favourably affected by the combination product.

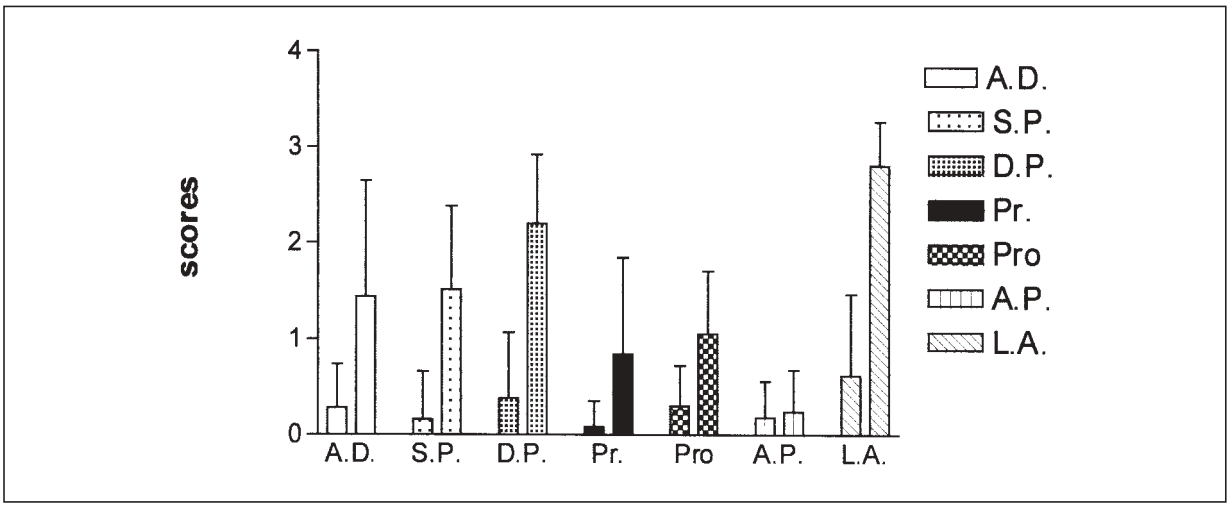

Figure 1. Comparison of the final values. (AD: anal discofort ($p < 0.0001$); SP: spontaneous pain ($p < 0.001$); DP: pain at defecation ($p < 0.0001$); Pr: proctorrhagia ($p < 0.0006$); Pro: proctitis (not significant); AP: anal prolapse ($p < 0.0001$); LA: local anesthetic consumption.

The combination drug was safe and well tolerated, and had no clinically significant effects on laboratory variables.

These findings support previous results obtained with the same combination drug given i.m. to relieve capillary impairment and venous insufficiency of the lower limbs, or given orally for hemorrhoids[5,7].

In conclusion, the efficacy and safety of Fleboside in the therapy of uncomplicated hemorrhoids was evidenced in this work. The rationale of the fixed combination emerged from the analysis of clinical results, suggesting that the synergy between the two active ingredients is able to better control the signs and symptoms of the disease, compared to the hemostatic component of the product alone.

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