

# Clinical Assessment of the Activity and the Tolerability of a *Triticum Vulgare* Extract-Containing Medical Device in Patients with Haemorrhoids

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**Abstract** Twenty outpatients suffering from symptomatic haemorrhoids were treated with a medical device in gel form containing watery extract of *Triticum Vulgare*, glycerine and Mucosave CG, given in three daily applications for 1-2 weeks. Signs and symptoms of haemorrhoids were evaluated at baseline (Visit 1) and after 1 (Visit 2) and 2 (Visit 3) weeks of treatment according to a 4-point rating scale (0 = absent, 1 = mild, 2 = moderate, 3 = intense). The primary variable of the study was the percentage of responder patients at Visit 2, defined as those patients in which the total Symptoms Score (TSS: sum of the scores of all symptoms) decreased at least 50% from the baseline value (V1). Two patients discontinued the treatment, one just before V2, inclusive of symptoms assessments, and another before V2 without evaluations. One patient did not attend V3. A decrease of at least 50% in TSS (i.e. a therapeutic success) was observed in 10 patients at week 1 and in 16 out of 17 patients at week 2. The mean TTS (mean baseline score: 8.47) decreased by 51% at week 1; a mean TTS score of 2 was observed at the end of study ( $p < 0.05$  vs baseline). Pain intensity and tenesmus were almost disappeared at the end of treatment. Improvements in burning and pruritus were evident just from week 1. Bleeding was present in almost all patients at baseline and greatly decreased from week 1. Mucorrhoea was present in 6 patients at baseline and disappeared during treatment. Interference with daily activities (mean baseline score: 1.8) significantly decreased at end of treatment (mean score: 0.4). No adverse events were recorded. The results of this study suggest that the device tested may represent an effective and safe method for the treatment of the haemorrhoids in symptomatic phase. (Study DAM/MD/001/12 approved by the Italian Ministry of Health).

**Keywords:** haemorrhoids, topical therapy, *triticum vulgare*

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## 1. Introduction

Haemorrhoids are enlarged anorectal vascular cushions. The cushions are conglomerates of blood vessels, supporting tissues and overlying mucus membrane or skin of the anorectal region. Haemorrhoids can be classified as internal or external in relation to the dentate line. Inflammation of such structures produce the clinical condition named haemorrhoids syndrome or haemorrhoids tout court [1,2]. The first known citation of this condition is reported in an Egyptian papyrus dated at around 1700 b.C [3]; a description is also reported in the Holy Bible [4]. The name came from the Latin haemorrhoidae, which in turn derives from the Greek αιμορροϊς, from αιμα (blood) and ρεο (flow). The haemorrhoids syndrome is characterized by pain, which may be associated with tenesmus, pruritus, local tumescence, mucous faeces and bleeding [5]. In case of external haemorrhoids the haemorrhoidal phlebectasia may be congested and

oedematous, with thrombi in some cases. Symptomatic haemorrhoids are a bothersome and common problem, although an exact estimation of incidence is difficult because patients have a tendency to use self-medication rather than to seek proper medical attention [6]. It is estimated that approximately half of adult people in Western countries, most frequently those aged between 45 and 65, suffer from haemorrhoids with variable symptoms; males and females patients are affected in similar manner [7]. It seems that haemorrhoids are most common in industrialised countries: evidence exist that this disease is rare in native tribes of Central Africa, thus suggesting that diet and lifestyle may be correlated with the development of haemorrhoids [8]. Constipation is probably the leading cause of haemorrhoids, as prolonged efforts produced for evacuation, particularly in case of hard faeces, determine an increase of abdominal pressure and hence a tendency to prolapse of rectal mucosa [9]. Conversely, repeated evacuations may account for a worsening of general conditions. Other important causes are familiarity,

hormonal conditions and the body position during the day (standing and right posture, or sitting at a desk for many hours in a day), poor physical activity, traumatic sports for the anal area (e.g. cycling and motorcycling), intense heat in the anal area (e.g. car seat left at the sunshine for many hours), intense efforts (cough, weights lifting, etc..) and – in some cases – stress [6]. Moreover, pregnancy is a condition at high risk of development or worsening of haemorrhoids [10]. Finally, a mention should be done for haemorrhoids due to more severe conditions, such as hepatic cirrhosis, portal vein thrombosis, rectum cancer. The therapy of haemorrhoidal syndrome is mainly based on a conservative approach, with the use of analgesics, vaso-protectants and local and systemic non-steroidal anti-inflammatory drugs [11]. Local treatments also include anaesthetics, steroids, surface protectants (e.g. vaseline, zinc oxide), flavonoids, calcium antagonists (in case of tenesmus) [12]. Surgical procedures are needed only in a minority of cases. Recently, a medical device in gel form (Farmaceutici Damor S.p.A, Naples, Italy) has been developed for the treatment of internal and external haemorrhoids, based on a watery extract of *Triticum Vulgare* (ETV), glycerol and Mucosave CG<sup>1</sup>. ETV improve the tissutal repair both at cutaneous and mucous level [13-16]; in case of disruption of the body surfaces act as protective layer, promoting the tissues healing. Glycerol exerts an emollient action. Mucosave, a mixture of vegetal extracts, show a cicatrizing and soothing action on the mucosae [17,18,19]. Therefore, the medical device arrange a protective lining on the damaged mucosa by means of its physical formulation and composition, thus contributing to the restore of the normal functional condition and to the regression of the inflammatory component, in addition to exerting a smoothing and refreshing effect. The aim of this study was to assess the protecting, smoothing, refreshing and tissutal repairing action of this product in the treatment of symptoms of haemorrhoidal syndrome, and to assess its local tolerability.

### 1.1. Ethics

The principles defined in the Declaration of Helsinki and following amendments were followed, and the Good Clinical Practices rules were applied. The investigator informed all participant patients about the study objectives and procedures, possible benefits and potential risks related to study participation. Both the Investigator and the patient signed and dated a double copy of the informed consent form before the patient took part in the study. The patient received one copy and the other one was archived in the study site together with the study documentation. The decision on taking part in the study was freely taken by the patient and it was clearly stated that the consent could be withdrawn at any time during the study, without penalties or loss of benefits for the patient. The study was approved by the pertaining Ethic Committee.

## 2. Patients and Methods

The study was conducted according to an open-label uncontrolled design in a group of 20 outpatients. The inclusion criteria were: both gender patients; age  $\geq 18$  and  $< 80$  years; presence of haemorrhoids (stage II>IV) in symptomatic phase; willingness to cooperate and ability to understand the study procedures and objectives; availability in taking part in the study and in adhering to experimental procedures as stated by signing the informed consent. The exclusion criteria were: pregnancy or breastfeeding; inadequate contraception in fertile women; history or evidence of metabolic or endocrine diseases (e.g. uncontrolled diabetes mellitus) or of any other local and/or systemic pathology possibly able to interfere with study parameters; concomitant treatment with antibiotics/antisepticals, steroidal and non-steroidal anti-inflammatory drugs, analgesics; concomitant treatment with antineoplastic and/or immunosuppressants; immunodeficiency states (e.g. HIV infection); neoplastic diseases; non-therapeutic use of psychotropic drugs; drug or alcohol abuse; neurological or psychiatric diseases that could impair the validity of the consent and/or the patient's adherence to study procedures; known allergy, hypersensitivity or intolerance to investigational product; any medical and non-medical condition that could significantly reduce the possibility to obtain reliable results, reach the study objectives, or complete the study; presumed patient's low cooperation; treatment with any investigational product in the last 30 days preceding the study.

The device was applied tid for 1-2 weeks; a baseline visit (V1), one intermediate visit after  $7 \pm 1$  days of treatment and a final visit (V3) after  $14 \pm 2$  days of therapy were performed. The intermediate visit could coincide with the final visit in case of disappearance or almost complete resolution of symptoms. The following symptoms were evaluated at any visit: pain, burning, pruritus, tenesmus, bleeding, mucorrhoea, interference with daily activities (e.g. working, driving etc..). Signs and symptoms were scored as 0 = absent, 1 = mild, 2 = moderate, 3 = intense (mild: intermittent, poorly bothersome; moderate: continuous, poorly bothersome; intense: continuous, very bothersome). To be eligible for study participation, patients were required to have at least two signs/symptoms with a score  $\geq 2$ . The tolerability of the device application was evaluated at each post-baseline visit. If requested, a re-check could be done at any time, even outside the scheduled visits. At the initial visit, the local inspection, rectal exploration and anoscopy (mucosal state of the lowest rectum, detection of haemorrhoidal varices, identification of fissures and fistula orifices) were performed. Anoscopy was done to exclude severe concomitant and not clinically evident diseases (e.g. neoplastic processes).

The primary variable of the study was the percentage of responder patients at V2, defined as those patients in which the total Symptoms Score (TSS: sum of the scores of all symptoms) decreased at least 50% from the baseline value (V1). The secondary efficacy variables of the study were the mean changes from baseline of TSS and of single signs and symptoms and the local tolerability of the product.

### 2.1. Statistical Analysis

<sup>1</sup> Composition: *Triticum vulgare* watery extract; glycerol; hydroxiethylcellulose; phenoxyethanol; Macrogol (polyethylenglicol) 400, Mucosave CG, distilled water.

The statistical analysis was performed by using the SAS<sup>®</sup>, version 9.2 (SAS Institute Inc. Cary NC, USA). Efficacy parameters were analysed in the intention-to-treat (ITT) population, which included all treated patients with post-baseline data, and in the per-protocol (PP) population, i.e. all ITT patients without major protocol violations. The tolerability was analysed in the safety population, i.e. all patients with evidence of at least one application of the device. Non-parametric tests were used in the analysis of results of TSS, by calculating the 95% confidence interval (CI) of changes from baseline and using the paired data Wilcoxon test (mean values were reported as descriptive statistics). Paired Wilcoxon test was used in the analysis of changes from baseline to V2 and V3 of semi-quantitative scores. The last observation carried forward (LOCF) approach was used for missing data at V3, by imputing data obtained at V2. The level of statistical significance was set at a p value < 0.05.

### 3. Results

Two patients discontinued the treatment, one just before V2, which was however performed inclusive of symptoms assessments, and another before V2 without evaluations. One patient did not attend V3.

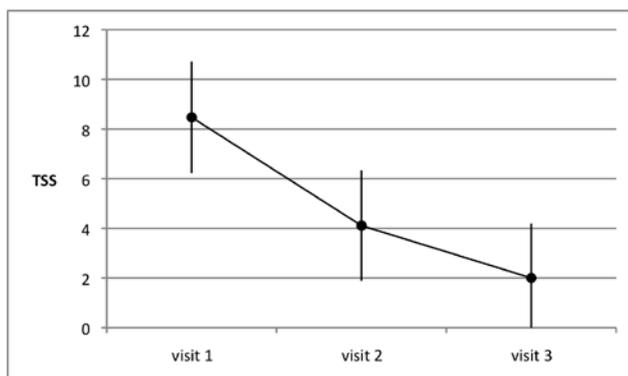
Table 1 shows the demographic and baseline characteristics of patients.

**Table 1. Demographic and baseline characteristics of patients**

age	min-max	38.5-73.6
(years)	mean±SD	59.2±10.2
gender	female	13 (65)
N(%)	male	7(35)
race N (%)	Caucasic	20(100)
Weight (Kg)	min - max	46-89
	mean ± SD	70±11
Height (cm)	min - max	150-181
	mean ± SD	167±8
BMI (Kg/cm2)	min - max	18.2-37.8
	mean ± SD	25.4±4.3

(SD: Standard Deviation; BMI: Body Mass Index)

No significant differences between the ITT and the PP analysis were found. A decrease of at least 50% in TSS (i.e. a therapeutic success) was observed in 10 patients at V2 and in 16 out of 17 patients at V3. The mean baseline TSS values was 8.47 and was reduced by 51% at V2; a mean TSS score of 2 was observed at the end of study. Changes from baseline were statistically significant (p<0.05). Figure 1 shows the values of TSS (sum of signs and symptoms) through the study.

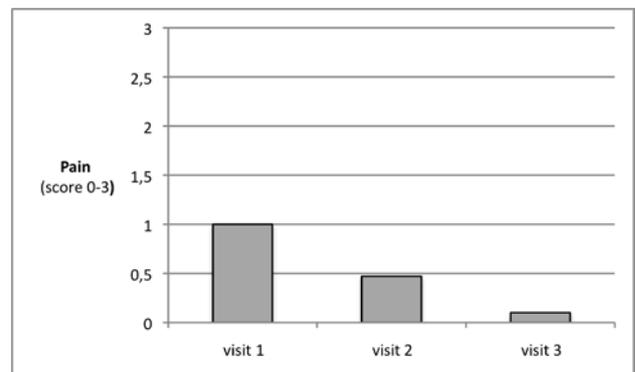


**Figure 1.** Total Symptoms Score (TSS); mean values and standard deviation

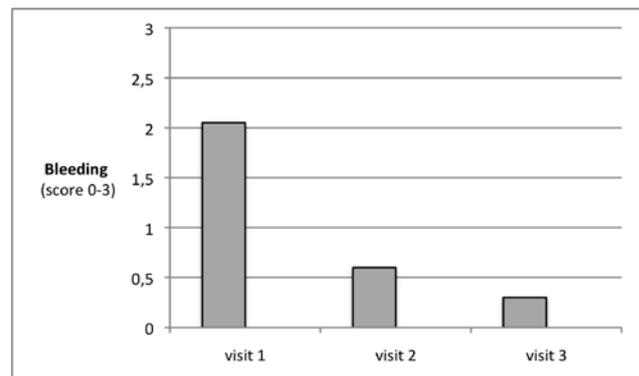
Pain intensity was greatly reduced at V2 and was almost disappeared at V3 (Figure 2). A similar pattern was observed for tenesmus, however present in a lower number of patients at baseline. Improvements in burning and pruritus was also evident just at V2. Bleeding, which was present in almost all patients at baseline, greatly decreased from V2 (Figure 3). Mucorrhoea was present in 6 patients at baseline and disappeared during treatment. Interference with daily activities (mean baseline score: 1.8) significantly decreased at V2, with a further improvement at V3 (mean score: 0.4).

### 4. Discussion

The presence of haemorrhoids in phlogistic phase is characterized mainly by pain, which may be associated with tenesmus, pruritus, local tumescence, mucous faeces and bleeding. The disease is very common in Western countries and causes not only discomfort, but also interference with working activity and daily living.



**Figure 2.** Pain; mean values; score 0-3



**Figure 3.** Bleeding; mean values; score 0-3

Although surgery is the definitive therapy, the therapeutic approach is conservative in most cases, mainly with the use of local treatments. Evidence exist that the *Triticum vulgare* watery extract-containing products are safe and effective for the treatment of various skin and mucous membranes lesions [13-16]. In particular, the beneficial effects of a mouth gel a lot alike the tested gel have been reported in the topical treatment of mucositis in cancer children [20]. In this study, the medical device was effective in reducing clinical symptoms of haemorrhoid syndrome. None of patients reported adverse events related to the application of the device. The results suggest that the tested *Triticum vulgare* extract-containing gel

medical device may represent an effective and safe approach for the management of haemorrhoids in symptomatic phase.

The main limits of the study are the small number of patients and the uncontrolled study design. However, the study was designed to preliminarily evaluate the efficacy and safety of a new medical device, not a drug. Therefore a quite small number of patients was judged as adequate to obtain clinically significant results. Furthermore, a “golden standard” for haemorrhoids local therapy is unavailable and a medical device having the same characteristics of the tested product is unavailable too. An open design was hence adopted. The results of this study may be the starting point for a larger, long-lasting, controlled, randomized clinical trial.

Dr Giovanni Finucci declare that there is no conflict of interest regarding the publication of this paper.

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