Original Article

A combination of diosmin, hesperidin, and ruscogenin: Clinical effects in symptomatic hemorrhoidal disease

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Abstract

Background: Phlebotonics are made of plant extracts and synthetic compounds. Although their mechanism of action is not completely clear, they are associated with an increase in venous tone and decreased capillary permeability. The aim of this paper was to assess the efficacy of Diosmin 500mg, Esperidine 90mg, Ruscogenin 100mg in improving symptoms of patients with hemorrhoidal disease.

Materials and Methods: This was an observational trial performed at the Department of Universitary General Surgery of L'Aquila from March 2021 to September 2021. Symptoms have been evaluated using scoring system proposed by Giordano *et al*. Patients have been clinically evaluated by the same surgeon at the time of diagnosis and at the 30th day of treatment.

Results: Seventy-one patients were included in the study. In Group A (study group) we reported a decrease in symptomatologic score of 50% with a 30-days follow-up, while we reported a decrease of 27% in Group B (control group). Among patients in Group A, 67% of those with grade IV hemorrhoidal disease have been re-stadiated to grade III after 30 days of treatment.

Conclusion: Flavonoids mixture could be a safe and effective mean for conservative management of hemorrhoidal disease. The doses seemed to be satisfactory and the proposed duration of treatment can be considered adequate.

Keywords: Diosmin, hesperidin, hemorrhoidal disease, phlebotonics, ruscogenin

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INTRODUCTION

Hemorrhoids are characterized by dilatation of the hemorrhoidal plexuses, weakness of supporting connective tissue, and inflammatory reaction. This is a very common condition which affects many people worldwide and represents an important clinical and social problem. Self-reported incidence of hemorrhoids in the USA is 10 million/year, corresponding to 4.4% of the population.[1,2] Anatomically, the hemorrhoids can be divided as external hemorrhoids (below the dentate line) and internal hemorrhoids (above the dentate line). The classification currently used to categorize this pathology is Goligher's system.[3] The acute clinical manifestation of hemorrhoidal disease is commonly known as "hemorrhoidal crisis," characterized by pain, bleeding, prolapse, edema, and thrombosis. Medical and conservative management is indicated for Goligher's

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Grade I or Grade II hemorrhoids and is based on diet and lifestyle modification.[4] Adequate fiber intake and phlebotonics are recommended by several national and international guidelines;[5,6] regular bowel activity and easy defecation can prevent prolapse and reduce bleeding.[7]

Phlebotonics are a heterogeneous class of drugs consisting of plant extracts and synthetic compounds. Although their mechanism of action is not completely clear, they are generally associated with an increase in venous tone, improved lymphatic drainage, and decreased capillary permeability, with an overall anti-inflammatory effect.[8,9] Several trials, reviews, and meta-analyses have demonstrated their role in control of bleeding, itching and soiling, symptoms commonly associated with hemorrhoidal disease.[8,10-12]

The aim of this paper was to assess the efficacy of the oral intake of a combination of diosmin 500 mg, hesperidin 90 mg, ruscogenin 100 mg (Mioven 700®) in improving symptoms of patients with symptomatic hemorrhoidal disease of II, III, and IV Grade and in acute hemorrhoidal crisis.

MATERIALS AND METHODS

This observational single-center trial was performed at the Department of University General Surgery of San Salvatore Hospital in L'Aquila, Italy, from March 2021 to September 2021. This study is approved from local Ethics Committee (approval number: 51380, 22.04.2021), and all patients gave their written informed consent to participate in the study.

Criteria of admitted patients were: Age >18; hemorrhoidal disease Graded II, III, or IV according Goligher's classification with the presence of symptoms or hemorrhoidal crisis.

Patients were divided into two groups. The study Group (A) was treated with two daily tablets of Mioven 700® for 10 days and then one daily tablet for the next 20 days, in association with one daily administration of Macrogol for 30 days. The second Group (B) was treated with one daily administration of Macrogol for 30 days and it was identified as the control group. For both groups of patients, we also recommended appropriate hygienic and behavioral measures: Warm sitz baths twice a day for 10 min and a balanced diet, limiting the consumption of alcohol and spices, and ensuring a sufficient intake of water.

After filling the informed consent, we asked patients to assign a score to the symptoms present at the time of diagnosis and therefore 30 days after the start of treatment. Symptoms have been evaluated using scoring system proposed by Giordano *et al*.[13] [Figure 1], according to which patients has to assess every parameter from 0 (absence of symptom) to 4 (daily symptoms). Moreover, patients have been clinically evaluated by the same surgeon at the time of diagnosis and at the 30th day of treatment, and their hemorrhoidal grade have been every time scored according to Goligher's classification. The main purpose of the present study was to observe symptoms' trend in patients treated with Mioven 700® for 30 days.

Statistical analysis

Clinical and demographical characteristics of the two groups were described using standard statistics. Discrete and nominal variables were expressed using frequencies and percentages, and the χ^2 was used to examine differences between the two groups. Continuous variables were expressed as median values and two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare patients. The significance of the within-group variation with respect to the primary outcome was evaluated using *t*-test for paired samples while differences between groups at the end of follow-up were evaluated using *t*-testy for independent samples. Linear regression was used to adjust the comparison with respect to baseline characteristics of the two groups. Statistical significance was set at an alpha value of 0.05. All statistical analyses were conducted using the statistical platform R statistical language (version 4.0.3; R Core Team, 2020).

RESULTS

Seventy-one patients were included in the study, of which 37 in the Group A (study group) and 34 in the Group B (control group). Of them, 42.25% were females and the mean age was 52 years old. No significant differences were observed between the two groups examined with respect to age ($P = 0.548$), sex ($P = 0.860$), and hemorrhoidal disease graded according to Goligher's classification ($P = 0.335$). Given the homogeneity of the two groups by age, sex, and grade of disease, these observations presumably

	Never	At least once per year	At least once per months	At least once per week	With every bowel movement
Bleeding	0	1	2	3	4
Prolapse	0	1	2	3	4
Manual reduction	0	1	2	3	4
Discomfort/pain	0	1	2	3	4
Impact on	Not at all	Minimal	Moderate	Severe	Very severe
QoL	0	1	2	3	4

Figure 1: Scoring system proposed by Giordano *et al*.

indicate that the sociodemographic and baseline clinical characteristics do not constitute confounding variables for a successful comparison of the two groups [Table 1].

In the Group A, we reported a decrease in symptomatologic score of 50% with a 30-days follow-up (from 9.6 to 4.5), while we reported a decrease of 27% in Group B (from 10.6 to 7.9) with the same follow-up [Figure 2]. At the clinical examination, among patients in Group A, 67% of those with Grade IV hemorrhoidal disease have been re-stadiated to Grade III after 30 days of treatment. Among patients of Group B, only 24% have been re-stadiated from IV to III Grade.

DISCUSSION

Hemorrhoidal disease is a very common condition which affects many people worldwide, regardless of age group. It is characterized by dilatation of the hemorrhoidal plexuses, weakness of supporting connective tissue, and inflammatory reaction.[2,9] Treatment options may include lifestyle modifications, medical treatment, office-based procedures, or surgical approach. Medical therapy has a central role, either as a primary treatment or as a bridge therapy before surgery. This role has been emphasized during the severe acute respiratory syndrome coronavirus 2 pandemic period, as surgical waiting lists have been postponed and consequently it has been necessary to find therapies to manage patients in this time frame.[14] The utility of phlebotonics has been widely underlined. They are generally associated with an increase in venous tone, improvement in lymphatic drainage, decrease in capillary permeability, with an overall anti-inflammatory effect.[7,9] Although their action is not completely understood, the main mechanism should be related to a scavenger of the hydroxyl radicals.

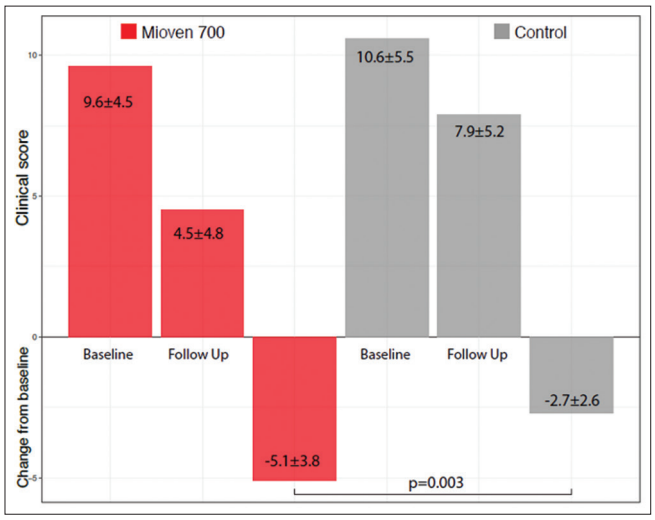

Figure 2: Graphic representation of the results, in terms of reduction of the symptomatological score

Our study aimed to investigate the effects of a combination of diosmin 500 mg, hesperidin 90 mg, ruscogenin 100 mg (Mioven 700®) in the treatment of the symptomatic hemorrhoidal disease graded II, III, and IV according Goligher's classification. We found that patients referred a clinical improvement, also verified by clinical examination by the same surgeon.

Diosmin is a natural bioflavonoid obtained by the dehydrogenation of the flavanone glycoside hesperidin. It shows some biological activities: It has antioxidant, anti-hyperglycemic, and anti-inflammatory effect,[15-17] with a favorable long-term safety profile.[18] Diosmin efficacy and safety were investigated in several clinical studies about ulcerative colitis, gastric ulcer, diabetes mellitus, hepatic fibrosis.[19-22] It is used to assist the treatment of hemorrhoids or chronic venous atherosclerosis diseases.[23] Hesperidin is found in the pericarp of citrus fruits. Its name is derived from the word "hesperidium" and it was first isolated in 1828 by French chemist Lebreton from the white inner layer of citrus peels.[24] Hesperidin, alone or in combination with other citrus bioflavonoids, is used for blood vessel conditions such as hemorrhoids, varicose veins. It has been related to protective effects against radiation-induced acute proctitis.[25] Ruscogenin was first isolated from Ruscus aculeatus and shows anti-inflammatory and antithrombotic activities. Due to antielastase activity and capillary permeability, it has been

Table 1: Descriptive analysis of demographic and baseline clinical characteristics of the sample

	Total (*n*=71), *n* (%)	Group A (*n*=37; 52.11), *n* (%)	Group B (*n*=34; 47.89), *n* (%)	*P*
Sex, *n* (%)				
Males	41 (57.75)	21 (56.76)	20 (58.82)	0.860*
Females	30 (42.25)	16 (43.24)	14 (41.18)	
Age, median	52	54	51	0.548**
Goligher classification, *n* (%)				
II	18 (25.35)	9 (24.32)	9 (26.47)	0.335*
III	31 (43.66)	19 (51.35)	12 (35.29)	
IV	22 (30.99)	9 (24.32)	13 (38.24)	

*Chi-square test, **Two-sample Wilcoxon rank-sum (Mann–Whitney) test

used in case of vasculitis and venous insufficiency.[26-28] Recent studies have shown that that Ruscus extract has binding affinity for muscarinic receptors particularly of M1 and M3 receptor subtypes. The activity of Ruscus extract at muscarinic receptors may contribute to its vasoprotective and anti-inflammatory effects.[29]

Our findings are supported by the literature

A meta-analysis conducted in 2012 showed how the use of phlebotonics has significant effects on bleeding, pain, and soiling commonly associated with hemorrhoidal disease.[8] Furthermore, a compound of diosmin and hesperidin has been reported to reduce rectal pain and bleeding, if used for the treatment of hemorrhoids, even after surgery,[10,30,31] and minimal adverse events are reported.[4]

In our study, we showed that flavonoids mixture is a safe and effective mean for conservative management of hemorrhoidal disease. The doses seemed to be satisfactory for the reduction of edema and for the improvement of painful symptoms. The proposed duration of treatment (30 days) can be considered adequate for the hemorrhoidal classes included in the study.

CONCLUSION

This study demonstrates as the use of Mioven 700® significantly improves symptoms and clinical conditions in patients with hemorrhoidal disease Graded II, III, or IV. It could be considered a useful strategy to conservatively manage this pathology, also in patients waiting for surgical intervention.

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Conflicts of interest

There are no conflicts of interest.

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