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New topical treatment of symptomatic internal hemorrhoids in a general practice setting

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ABSTRACT

Introduction: Oral usage of flavonoid-based drugs can be successfully applied in the conservative treatment of internal hemorrhoids; however, its efficiency in the form of topical preparations has not been demonstrated yet. The present study aimed to determine the efficiency of ointment with propolis extract (containing minimally 115 mg/kg of flavonoid galangin) in relief and suppression of the symptomatic internal hemorrhoids Grade 1 and 2 (bleeding, prolapse, pain, and itching).

Methods: This prospective cohort epidemiological study that included 46 participants of both the genders, mean age 53.6 ± 14.3 years, was conducted in the general practice setting in Osijek, Croatia, and lasted for three months. A specially designed questionnaire was used to collect demographic data and data concerning the hemorrhoid disease symptoms and to evaluate the intensity of the latter data according to the scale defined in the research protocol.

Results: The study showed statistically significant improvements in the intensity of all the symptoms connected with the internal hemorrhoid Grades 1 and 2 ($p < 0.001$) during the follow-up period, as well as statistically significant differences in proportions of participants with and without of the each of the analyzed symptoms before and after the therapy ($p < 0.001$). After three months of treatment with ointment containing propolis extract, 82.7% of patients (38/46) had none of the analyzed symptoms.

Conclusions: Ointment with propolis extract efficiently affected all the analyzed symptoms of the hemorrhoid disease, thus having a very significant place within the conservative treatment of hemorrhoids.

Key words: Hemorrhoids; topical treatment; propolis; flavonoid; Croatia

INTRODUCTION

Hemorrhoid disease is a common problem that is managed by various physicians, ranging from primary care providers to the surgeons (1). Prevalence of symptomatic hemorrhoids varies from 4.4% in the general population to 36.4% in the general practice (2-5). It has been estimated that 50% of the population has hemorrhoids by the age of 50 years (6). The annual rate of office visits for hemorrhoids is twelve for every 1000 patients in the United States; its prevalence is similar between the sexes and increases with age until the seventh decade (3,7). Only one of three patients with symptomatic hemorrhoids seeks medical help (3).

Hemorrhoids are classified as internal, external, and mixed, based on their site of origin (8). External

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hemorrhoids begin below the dentate line, while internal hemorrhoids originate above the dentate line (2,3,8). Mixed hemorrhoids can indicate lesions that arise at the dentate line, or the term can be used to describe the presence of both internal and external hemorrhoids (8). Internal hemorrhoids are divided into four categories depending on the grade of prolapse: Grade 1 - protrudes into the anal canal but does not prolapse, Grade 2 - prolapses but reduces spontaneously, Grade 3 - prolapses and requires manual reduction, and Grade 4 - irreducible prolapse (2,3,8-10).

Symptomatic hemorrhoids are treated either medically or mechanically (11). External hemorrhoids are usually symptomatic in cases when they are thrombosed, and the most appropriate treatment in such cases is the surgical one (incision under local anesthetic to remove the clot) (8). The most common symptoms of internal hemorrhoids are bleeding and prolapse. Less frequently, symptoms also include pain and itching (3). Medical therapy is commonly used for symptomatic internal hemorrhoids of Grades 1 and 2, while mechanical treatment is used for Grades 3 and 4 and Grades 1 and 2 refractory to medical treatment (11). Primary care physicians can safely use simple treatment measures to manage most cases of symptomatic internal hemorrhoids (3).

Among the non-surgical treatment of symptomatic internal hemorrhoids in the primary healthcare setting, the various topic treatments are most frequently used. These topic preparations often contain anesthetics, corticosteroids, and anti-inflammatory agents in varying proportions. Most of these products help to maintain personal hygiene and alleviate symptoms (12,13).

Propolis is a resinous substance collected by honeybees from various plant sources. It is used by the bees to protect the nest entrance against intruders and bacteria. Since ancient times, it has been used as a traditional monastic, folk and natural medicine in many countries. In recent studies, a wide range of pharmacological properties were demonstrated for this substance, including antibacterial, antiviral, antifungal, antioxidant, antitumor, adstringent, and anti-inflammatory activity with the latter one been especially emphasized (14,15). Flavonoids and phenol acids in propolis represent the main compounds responsible for its various curative effects (16). In recent years, there have been some attempts in the oral usage of flavonoid-based drugs, such as venotonic flavonoid micronized purified flavonoid fraction (MPFF), in the conservative treatment of internal hemorrhoids that all concluded how these substances could be considered an effective and well-tolerated agent in the treatment of acute episodes of hemorrhoids (17-22). Besides that, there is also the study which had investigated potential clinical use of MPFF for the treatment of symptoms after hemorrhoidectomy with the conclusion that MPFF used in combination with short-term antibiotic and anti-inflammatory medication can reduce both the duration and extent of post-operative symptoms and wound bleeding following hemorrhoidectomy (23). Since now, there have not been prospective studies that evaluate the efficiency of topic preparations with propolis extract containing flavonoids in the reduction of internal hemorrhoids symptoms.

The aim of the present study was to determine the efficiency of ointment with propolis extract (that contains minimally 115 mg/kg of flavonoid galangin) in relief and suppression of the symptomatic internal hemorrhoid Grades 1 and 2 (bleeding, prolapse, pain, and itching) and its efficiency in preventing the relapse of these symptoms.

METHODS

Study design and ethical approval

This study was designed as a prospective cohort epidemiological study and was conducted in the general practice setting in Osijek, Croatia.

The local ethics committee approved the study protocol. Before the enrolment in the study, each participant had been explained the main objective of the study in details and was asked to sign the written informed consent for his or her participation in this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Participants

The study included 46 participants of both gender, mean age of 53.6 ± 14.3 (range 23–80 years), who are suffering from the symptoms of internal hemorrhoid Grades 1 and 2 (bleeding, prolapse, pain, and itching) for which they had been treated by their chosen general practitioner.

Criteria for inclusion of the participants in the study were as follows: Patients aged between 18 and 80 years suffering from the acute symptoms of internal hemorrhoid Grades 1 and 2 (bleeding, prolapse, pain, and itching). Allowed co-occurring illnesses were hypertension, obesity, and varicose veins.

Criteria for exclusion participants from the study were as follows: Patients older than 80 years or younger than 18 years suffering from acute symptoms of the internal hemorrhoid Grades 1 and 2, patients suffering from symptoms of the internal hemorrhoid Grades 3 and 4, pregnant women suffering from hemorrhoids, patients suffering from liver cirrhosis, patients suffering from some inflammatory bowel disease or patients suffering from colorectal carcinoma, patients with anal fissure, patients suffering from hemorrhoids who had been using any topical product or ointment with propolis extract to facilitate their symptoms during 1 month before the beginning of this survey, patients suffering from hemorrhoids who had been using any other topical product or ointment to facilitate their symptoms during 1 month before the beginning of this survey, patients who are continuously using non-steroid anti-inflammatory drugs, patients that are using corticosteroids, patients who are under some kind of anticoagulant therapy, and patients who are under cytostatic treatment or undergo radiation treatment.

Study protocol

All participants got the free sample of ointment with propolis extract for facilitating and suppression of their symptoms together with the detailed instructions for the use of this product from their chosen general practitioner. The ointment contained vaseline, lanolin, propolis extract (with minimally 115 mg/kg of flavonoid galangin), and chamomile extract. The participants had been instructed to use this prescribed therapy until the stop of acute symptoms 3 times/day and after that for the prevention of relapse of these symptoms all together 3 months, 1 time/day.

During the enrolment of the participants in the study (first contact with the physician), the participants had been asked to fill out the questionnaire providing the basic demographic and anamnestic data such as age, gender, duration and intensity of symptoms, and family history of hemorrhoids. Each symptom was scored on a graded severity scale from 0 to 3 (where 0 means without symptom, 1 means mild symptom, 2 means moderate symptom, and 3 means heavy symptom).

Each participant that had been included in the study was monitored during 3 months, and the evaluation of his or her symptoms has been done at the day of his or her enrolment in the study (0 status) and 1, 2, and 3 months after the continuous therapy. The evolution of symptoms (bleeding, prolapse, pain, and itching) during the follow-up period was assessed by means of patients' self-questionnaires. Each symptom was scored on a graded severity scale from 0 to 3 where 0 means without symptom, 1 means mild symptom, 2 means moderate symptom, and 3 means heavy symptom.

Statistical analysis

Descriptive statistics were used for data processing and analyzed using the SPSS Statistical Package for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). The subsequent results are presented in tables. Friedman's test was used to compare mean scores for each symptom analyzed (bleeding, prolapse, pain, and itching) during the follow-up period and McNemar's test was used to determine differences in proportions of patients with and without of the each of analyzed symptom before and after the therapy. On all statistical analyses, two-sided $p = 0.05$ were considered to be statistically significant.

RESULTS

The mean age of all study participants was 53.6 ± 14.3 years (range 23–80). Among them, there were 24/46 males (52.2%) and 22/46 females (47.8%). According to the grade of internal hemorrhoids that they are suffering from, there were 23/46 (50.0%) participants with internal hemorrhoid Grade 1 and 23/46 (50.0%) participants with

internal hemorrhoid Grade 2. Mean duration of the participants' symptoms connected with internal hemorrhoid Grades 1 and 2, from which they were suffering, was 4.0 ± 1.8 years. According to the presence or the absence of family history of hemorrhoids, there were 27/46 (58.7%) participants with the positive family history of hemorrhoids and 19/46 (41.3%) participants with the negative family history of hemorrhoids.

In the study population, Friedman's tests showed statistically significant improvements in the intensity of their symptoms connected with the internal hemorrhoid Grades 1 and 2 that they were suffering from (bleeding, prolapse, pain, and itching) during the follow-up period (Table 1).

McNemar's test showed statistically significant differences in proportions of participants with and without of the each of the analyzed symptoms before and after the therapy (Table 2).

When looking at the number of patients with different numbers of symptoms before the therapy and after the therapy, the large decrease in the number of patients with more than one symptom of hemorrhoid disease and the large increase in a number of patients without any symptoms were seen (Table 3). The increase in the number of patients from two patients with one symptom before the therapy to three patients with one symptom after the therapy is a result of decreased number of patients with more than one symptom after the therapy because some of the patients with more symptoms were left with only one symptom due to the therapeutic efficiency.

DISCUSSION

Patients suffering from the symptomatic internal hemorrhoid Grades 1 and 2 that include bleeding, prolapse, pain, and itching had clinically useful benefits when treated with the ointment containing propolis extract (with minimally 115 mg/kg of flavonoid galangin). During the study period, the large decrease in the intensity or the complete disappearance of the analyzed symptoms has occurred in all the patients, and none of the patients have reported the exacerbation or the relapse of any of the symptoms. After the therapy with ointment containing propolis extract, there were 82.7% of patients (38/46) that were complete without any of the analyzed symptoms.

Some recent studies have shown how oral usage of flavonoid-based drugs can be successfully applied in the conservative treatment of internal hemorrhoids (17-22) and also as an adjunct therapy in the patients after the hemorrhoidectomy (23). However, its efficiency in the form of topic preparations intended for patients suffering from the symptomatic internal hemorrhoid Grades 1 and 2 has not been demonstrated, which was the main reason for the present study.

Although the various topic treatments are most frequently used among the non-surgical treatments of symptomatic internal hemorrhoids in a primary health-care setting, no rigorous evidence exists to support the use of the topical therapies due to the lack of proper conducted scientific studies (3). Patients had reported some practical benefit with the use of the topical agents containing corticosteroids and anesthetics (7). When administering those to patients, one should always advise them against the prolonged use of these agents due to the possible local allergic effects and the sensitization of skin (3). In the present study, ointment with propolis extract efficiently affected all the analyzed symptoms of the hemorrhoid disease (bleeding, prolapse, pain, and

TABLE 1. Comparison of the mean scores for each analyzed symptom (bleeding, prolapse, pain, and itching) among the study participants during the follow-up period

Symptom	Status before the therapy (0 status)	Status after 1 month of therapy	Status after 2 months of therapy	Status after 3 months of therapy	*p-value*
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Bleeding (*n*=46)	1.24±0.673	0.30±0.591	0.11±0.434	0.07±0.327	<0.001*
Prolapse (*n*=46)	1.48±1.005	0.39±0.682	0.20±0.542	0.17±0.529	<0.001*
Pain (*n*=46)	1.46±0.959	0.43±0.779	0.15±0.420	0.11±0.379	<0.001*
Itching (*n*=46)	1.50±1.027	0.46±0.751	0.20±0.453	0.15±0.420	<0.001*

*Friedman's test

TABLE 2. Patients with and without the analyzed symptoms (bleeding, prolapse, pain, and itching) before and after the therapy

Symptom	Status before the therapy		Status after the therapy		*p-value*
	Patients with Symptom	Number of patients without symptom	Number of patients with symptom	Number of patients without symptom	
Bleeding (*n*=46)	41	5	2	44	<0.001*
Prolapse (*n*=46)	37	9	5	41	<0.001*
Pain (*n*=46)	39	7	4	42	<0.001*
Itching (*n*=46)	38	8	6	40	<0.001*

*McNemar's test

TABLE 3. Participants according to the number of the symptoms of hemorrhoid disease before and after the therapy

Number of patients with a different number of symptoms of hemorrhoid disease	Before the therapy (%)	After the therapy (%)
Patients with 4 symptoms	28 (60.9)	1 (2.2)
Patients with 3 symptoms	9 (19.6)	2 (4.3)
Patients with 2 symptoms	7 (15.2)	2 (4.3)
Patients with 1 symptom	2 (4.3)	3 (6.5)
Patients without symptoms	0	38 (82.7)
Total	46 (100.0)	46 (100.0)

itching) without any side effects, during the relatively long period of time (3 months), thus allowing its prolonged usage as a preventive measure that may prevent time-consuming and expensive complications of the disease.

Animal studies have shown that the flavonoids reduce the activation of the neutrophils, mediate the inflammation, and decrease the soluble endothelial adhesion molecules (24-25). Human trials have shown the ability of the flavonoids to improve the venous tone and the vein elasticity assessed by the plethysmography and to decrease the plasma markers of the endothelial activation (25-27). It has also been proven that the flavonoid fraction improves the lymphatic drainage and reduces the capillary hyperpermeability by protecting the microcirculation from inflammatory processes (28,29). Due to all that, the micronized purified phlebotropic flavonoid fraction was approved as an orally administered agent for the medical treatment and is today a common and a quite popular alternative treatment for hemorrhoids in Continental Europe and the Far East (29).

CONCLUSIONS

The present study offers the sound evidence that flavonoids are equally efficient in the relief and the suppression of symptomatic internal hemorrhoid Grades 1 and 2 when applied topically through the ointment containing the propolis extract, which represents the highly efficient new approach in the conservative treatment of hemorrhoids.

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