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The effectiveness of combined topical product with fluocortolone pivalate and lidocaine for hemorrhoids: results of a multicenter observational study

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ABSTRACT *AIM: to assess the changes in hemorrhoids symptoms and satisfaction with treatment against the background of treatment with a combined topical product Relief® Pro.*

PATIENTS AND METHODS: multicenter prospective non-interventional cohort study was done in 13 clinical centers in Russia. The study included patients aged 18 to 65 years with acute hemorrhoids of stages 1–2 treated with the combined product Relief® Pro (rectal suppositories, cream or a combination thereof). The follow-up period was up to 14 days (in the case of 2 visits to the clinical center after receiving the initial data). The analysis was performed on the basis of data obtained at Visit 2 (5–7 days of therapy) and Visit 3 (10–14 days of therapy) vs the initial data (Visit 1). Following criteria were used: the severity of hemorrhoid symptoms on the Sodergren scale, the severity of hemorrhoid symptoms (pain, bleeding, itching, edema, the presence of discharge, a feeling of discomfort), the size of the largest hemorrhoid node, the satisfaction of the doctor and the patient with treatment, assessment of the patient's adherence to recommendations for lifestyle changes and treatment, evaluation of the use of the drug Relief® were evaluated as endpoints About the treatment process and patient preferences regarding the dosage form of the prescribed drug. In addition, adverse events were evaluated.

RESULTS: the study included 1000 patients aged 18 to 65 years (men — 54.5%, women — 45.5%) Patients had grade 1 acute hemorrhoids (330 patients), grade 2 acute hemorrhoids (345 patients) and exacerbation of chronic hemorrhoids (325 patients). The drug Relief® Pro rectal cream was used by 333 patients; suppositories — 383 patients; joint therapy with both dosage forms — 284 patients. During follow-up (visits 2 and 3), positive dynamics was observed in patients — a decrease in the severity of hemorrhoid symptoms both during objective examination and according to patient questionnaires. So, according to the patients' estimates, the use of Relief® Pro, regardless of the form, led to a decrease in the severity or disappearance of the main symptoms of hemorrhoids — bleeding, itching, edema, the presence of discharge, discomfort already by Visit 2 and in almost all patients by the end of observation.

A similar change of the symptoms due the digital examination: by day 5–7, the severity of edema and bleeding in the perianal region, bleeding decreased. About 96% of patients and about 97% of doctors were satisfied with the treatment. Application of both forms of Relief® The ABM was characterized by good tolerability: there were no adverse events associated, according to the researcher, with the studied drug.

CONCLUSIONS: combined topical product Relief® Pro is effective for hemorrhoids.

KEYWORDS: *hemorrhoids, observational study, lidocaine, fluocortolone pivalate, Relief Pro*

CONFLICTS OF INTERESTS: *the study was organized and financed by Bayer Company*

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KEY THESES

What is already known about the subject?

- Modern algorithms for the treatment of hemorrhoids recommend symptomatic treatment with topical combined medications. However, their clinical efficacy may vary depending on the dosage form or dosage of active substances in a particular drug.
- One of the combined drugs used in the treatment of acute hemorrhoids, which includes GCS (fluocortolone pivalate) and a local anesthetic (lidocaine hydrochloride), is Relief® Pro. The drug has been approved for medical use since 1986 and is currently used in various countries around the world.

Relief® Pro has been the subject of a number of studies. However, there were no data on the use of the drug Relief® Pro in a large number of patients in real clinical practice.

What is new in this study?

- Data on the efficacy and safety of a combined drug containing flucortolone pivalate and lidocaine in the form of rectal cream and suppositories in patients with acute hemorrhoids of the 1–2 degree obtained from real practice.

How can this affect clinical practice?

- The results of this study confirm the significant efficacy and safety of the Relief® Pro both as a rectal cream and as suppositories, as well as their combinations for the treatment of acute hemorrhoids and exacerbation of chronic hemorrhoids.

INTRODUCTION

Hemorrhoids are one of the most common human diseases and the most common reason for contacting a coloproctologist.

The prevalence of the disease in the Russia is 130–145 people per 1,000 adult population (13.0–14.5%), and its specific weight in the structure of coloproctological diseases ranges from 34% to 41% [1–5,18]. This pathology is equally common in men and women. It is known that the incidence of hemorrhoidal disease increases with age [6] and is most often observed between 30 and 60 years. However, it can develop at any age, even in childhood [7].

Risk factors for the development of hemorrhoids traditionally include chronic constipation, pregnancy, heredity, high socio-economic status, chronic diarrhea, malignant colorectal tumors, liver diseases, obesity, increased resting pressure of the anal canal, decreased rectal muscle tone, condition after rectal surgery, and episiotomy [8,9]. The modern style of life is accompanied by increased physical inactivity.

Forced prolonged sitting (at the computer in the office and at home, driving a car, etc.) is accompanied by stagnation of blood circulation in the pelvic organs, and primarily in the rectum.

This in turn leads to an increase in the incidence of hemorrhoids, which increasingly affects people of young age [1–5].

According to the clinical guidelines of the Association of Coloproctologists of Russia [18], diet treatment, conservative treatment, minimally invasive and incisional surgery and their combinations are used for the hemorrhoids, depending on the stages.

Elimination of constipation due to the inclusion of a sufficient amount of dietary fiber and water in the diet is the most important and necessary condition for the successful treatment of hemorrhoids. At the same time, conservative treatment aimed only at normalizing the activity of the gastrointestinal tract is not an independent effective method of treating hemorrhoids.

Conservative drug treatment should include oral and topical medications. Oral administration of rutoside, diosmin, centella asiatica, flavonoids, plant extracts reduce the fragility of capillaries and improves microcirculation in venous insufficiency [10].

Topical drugs with analgesic and anti-inflammatory effect provide rapid relief of the main symptoms of hemorrhoids — discomfort, itching, pain and bleeding.

Despite the increasing use of surgical techniques for the treatment of hemorrhoids, topical drugs are used in clinical practice as symptomatic agents.

Invasive treatments such as sclerotreatment, coagulation, ligation of nodes and incisional surgery

are recommended in situations where hemorrhoid symptoms affect the patient's quality of life [8,9]. Each case of hemorrhoidal disease is polyetiological, usually has a chronic character and often requires an individual treatment regimen.

The main objectives of local treatment are to relieve the symptoms of the disease and return the patient to normal life. Drugs for symptomatic local treatment of hemorrhoids are indicated at all stages. Such drugs include steroid and nonsteroidal anti-inflammatory drugs, local anesthetics, astringents and emollients or combinations thereof [9]. Most of them help the patient maintain personal hygiene and relieve itching and pain. The most commonly used forms of drugs in proctology are creams and ointments for the perianal and anal areas and rectal administration, as well as rectal candles.

Topical drugs for the treatment of hemorrhoid symptoms, including pain and itching, often contain local anesthetics, which for a certain time provide local loss of sensitivity (anesthesia) in the area of application of the drug.

Benzidamine and lidocaine are among the most commonly used topical anesthetics in proctology [1–3,18].

Some topical antihemorrhoidal drugs contain steroids, which have anti-inflammatory, anti-allergic and antipruritic effects.

Steroids diffuse into cells and bind to steroid receptors in the cytoplasm, forming a steroid-receptor complex [11]. The activated complex binds to specific DNA sequences and modifies gene transcription, which ultimately affects the synthesis of inflammatory mediators [12]. As a result, capillary dilation, intercellular edema and tissue infiltration decrease, capillary proliferation is suppressed [13].

Currently, local antihemorrhoidal drugs containing fixed combinations of steroids (hydrocortisone, fluorocortolone) and local anesthetic (cinchocaine, lidocaine) have been widely used in clinical practice. Such combinations quickly and effectively relieve symptoms and improve the quality of life of patients [15–17]. Since the mechanism of action of steroids is realized through gene expression and suppression of the synthesis of cellular proteins, their effect cannot occur instantly. And in this case, a combination with a fast-acting local anesthetic is important, which provides relief of pain and itching immediately after application.

In addition to the dual mechanism of action, combined drugs have another important advantage: it is easier for the patient to use 1 combined agent, rather than each of them separately, which facilitates compliance with the treatment regimen. In addition, a fixed combination of active ingredients guarantees the use of components in the required proportions and dosages.

Description of the Study

A prospective multicenter non-interventional study was conducted to evaluate the effectiveness of one of the drugs for local hemorrhoid treatment — a fixed combination of fluocortolona pivalate and lidocaine — and other aspects of the treatment of hemorrhoidal disease.

The study was conducted in the period from November 2018 to October 2019 in 13 clinical centers located in 8 cities of the Russian Federation: Moscow, St. Petersburg, Yaroslavl, Smolensk, Rostov-on-Don, Astrakhan, Ryazan, Kursk. 44 coloproctologists participated in the study.

GOALS AND OBJECTIVES

The main purpose of the study was to evaluate effect of the use of 2 dosage forms (rectal cream and rectal suppositories) of the combined drug Relief® Pro (fluocortolona pivalate + lidocaine) in real clinical practice.

To achieve this goal, the following parameters were studied: the dynamics of the main symptoms of hemorrhoids during the treatment; the change in the size of the largest hemorrhoid node during treatment; patients' compliance to the doctor's recommendations; satisfaction of the doctor and the patient with the treatment with Relief® Pro; patients' preferences regarding the dosage form of the prescribed drug and the consumer properties of these dosage forms.

Design

This was a prospective multicenter non-interventional cohort study involving patients with acute hemorrhoids of the 1–2 degree or exacerbation of chronic hemorrhoids, to whom the attending

Table 1. *Demographic indicators (n = 1000)*

Demographic indicators	The value of the indicator in different subgroups of treatment		
	Relief® Pro cream (*n* = 333)	Relief® Pro suppositories (*n* = 383)	Relief® Pro cream + suppositories (*n* = 284)
Gender			
Male, *n* (%)	183 (55.0%)	217 (56.7%)	145 (51.1%)
Female, *n* (%)	150 (45.0%)	166 (43.3%)	139 (48.9%)
Age, years			
Mean	40.7 ± 10.8	41.8 ± 11.1	41.4 ± 10.7
Median	39	41	40
Minimum — Maximum	19–65	20–66	18–65
Height, cm			
Mean	171.4 ± 8.8	172.7 ± 8.8	172.2 ± 8.2
Median	172	174	173
Minimum — Maximum	150–197	150–196	150–192
Body weight, kg			
Mean	74.2 ± 13.7	76.9 ± 13.7	75.3 ± 13.5
Median	74	78	75
Minimum — Maximum	48–120	49–130	50–125

physician, as part of routine clinical practice, prescribed a fixed combination drug containing fluocortolone pivalate and lidocaine for local treatment.

The patient independently decided whether to follow the doctor's prescription and follow other recommendations (lifestyle changes, diet, etc.). The patient could change his mind (for example, in a pharmacy) and buy another available drug(s) or even ignore all prescriptions and recommendations of the doctor, completely refusing treatment. If the patient decided not to use the prescribed drug, no further information about the patient was collected.

Patients were included in the study at the initial treatment if they met the inclusion criteria and signed an informed consent (Visit 1). It was assumed that after the first visit, the patient would come for follow-up examinations twice within the next 10–14 days: Follow-up Visit 2 (Day 5–7) and Follow-up Visit 3 (Day 10–14).

The non-interventional design of the study was chosen as the most suitable for evaluating the effectiveness of the Relief® Pro in modern real clinical practice. Unlike interventional studies, the design of non-interventional (observational) clinical trials does not provide for randomization and 'blinding', and the selection of patients is not based on strict inclusion/non-inclusion criteria. Such a design also has certain limitations (for example, it is impossible to compare it with another drug). However, taking into account the objectives of this study, this methodology allowed to obtain a sufficient data of interest.

All the data obtained during the study were obtained from a set of manipulations performed by a doctor during a standard coloprotological appointment and examination.

In addition, at each visit, additional information was collected from patients in the form of filling out a questionnaire or providing data from the patient's diary — 'Patient Reported Outcome' (PRO).

Study Population

1,001 patients were included in the study, 1 patient dropped out at the screening stage, 1,000 patients completed the study — 545 (54.5%) men and 455 (45.5%) women aged 18 to 65 years.

For each participant of the study, the dosage form, dose and dosage regimen of the drug Relief® Pro was selected in accordance with the approved instructions for medical use and taking into account the indications, as well as based on the personal preferences of the research doctor or the preferences of the patient.

The decision on the appointment of treatment was made before the patient was included in the study.

To analyze the data, patients were divided into subgroups according to the prescribed dosage form of the drug — cream, suppositories or a

Table 2. *Data on the distribution of diagnoses and forms of hemorrhoids, initial data*

Data on the initial pathology	The value of the indicator in different subgroups of treatment		
	Relief® Pro cream (*n* = 333)	Relief® Pro suppositories (*n* = 383)	Relief® Pro cream + suppositories (*n* = 284)
Diagnosis			
Acute hemorrhoids of the 1 degree — Node thrombosis without inflammatory reaction, frequency (%)	152 (45.6%)	134 (35%)	44 (15.5%)
Acute hemorrhoids of the 2nd degree — Thrombosis of nodes with their inflammation, frequency (%)	145 (43.5%)	67 (17.5%)	133 (46.8%)
Exacerbation of chronic hemorrhoids, frequency (%)	36 (10.8%)	182 (47.5%)	107 (37.7%)
The form of hemorrhoids			
Internal hemorrhoids, frequency (%)	5 (1.5%)	253 (66.1%)	24 (8.5%)
External hemorrhoids, frequency (%)	318 (95.5%)	58 (15.1%)	137 (48.2%)
Combined hemorrhoids, frequency (%)	10 (3%)	72 (18.8%)	123 (43.3%)

combination thereof. The patients in the subgroups were comparable in age, height and weight (Table 1).

The patients were diagnosed with acute hemorrhoids of the 1–2 degree (with thrombosis of external/internal/external + internal nodes, including cases of bleeding) in accordance with the Goligher classification of acute hemorrhoids — with acute hemorrhoids of the 1st degree (330 patients), 2nd degree (345 patients) and exacerbation of chronic hemorrhoids (325 patients) (Table 2).

Groups of patients who used different dosage forms of Relief® Pro were not statistically balanced in terms of diagnosis and form of the disease: patients with nodular thrombosis without an inflammatory reaction (acute hemorrhoids of the 1st degree) were most often prescribed Relief® Pro cream (*n* = 152, 46.1%), less often — Relief® Pro suppositories (*n* = 134, 40.6%); patients with nodular thrombosis with their inflammation (acute hemorrhoids of the 2nd degree) were more often prescribed Relief® Pro cream (*n* = 145, 42.0%) or a combination of Relief® Pro cream + suppositories (*n* = 133, 38.6%); patients with exacerbation of chronic hemorrhoids were more often prescribed Relief® Pro suppositories (*n* = 182, 56%), less often — a combination of Relief® Pro cream + suppositories (*n* = 107, 32.9%).

It is obvious that the prescription of a particular dosage form of the drug Relief® Pro was carried out depending on the form of hemorrhoids: the external form of hemorrhoids was more often treated with Relief® Pro cream (*n* = 318, 62.0%); the internal form — with Relief® Pro suppositories (*n* = 253, 89.7%); the combined form — with a combination of Relief® Pro cream + suppositories (*n* = 123, 60%).

The study did not include patients with at least one of the following conditions/states: the participation of the patient in research programs involving manipulations that go beyond routine clinical practice; acute hemorrhoids of the 3d degree, contraindications to the use of the drug Relief® Pro listed in the approved instructions for medical use, in the presence of anemia and/or severe/profuse bleeding from hemorrhoids; after surgery in the perianal area (in anamnesis); concomitant treatment with antibacterial drugs, anticoagulants and antiplatelet agents, antitumor drugs and/or immunosuppressors; in the case of inflammatory bowel diseases, severe or acute liver disease; colorectal cancer, purulent-inflammatory diseases of the perianal area or anal canal.

PATIENTS AND METHODS

The study included patients who were prescribed the drug Relief® Pro as part of routine clinical practice in one or both dosage forms:

- Rectal cream: 1 mg/g of Fluocortolone + 20 mg/g of Lidocaine
- Rectal suppositories: 1 mg of Fluocortolone + 40 mg of Lidocaine

For each participant in the study, the dosage form, dose and dosage regimen of the drug Relief® Pro

Table 3. *The occurrence of some of the most common risk factors in the medical history of patients (n = 1000)*

Presence of a risk factor	The value of the indicator in different subgroups of treatment		
	Relief® Pro cream (*n* = 333)	Relief® Pro suppositories (*n* = 383)	Relief® Pro cream + suppositories (*n* = 284)
Risk factors: Family anamnesis			
Yes, *n* (%)	90 (27.0%)	151 (39.4%)	36 (12.7%)
No, *n* (%)	243 (73.0%)	232 (60.6%)	248 (87,3%)
Risk factors: Sedentary work			
Yes, *n* (%)	185 (55.6%)	188 (49.1%)	157 (55.3%)
No, *n* (%)	148 (44.4%)	195 (50.9%)	127 (44.7%)
Risk factors: Work associated with heavy physical exertion			
Yes, *n* (%)	54 (16.2%)	52 (13.6%)	74 (26.1%)
No, *n* (%)	279 (83.8%)	331 (86.4%)	210 (73.9%)
Risk factors: Constipation			
Yes, *n* (%)	145 (43.5%)	223 (58.2%)	108 (38.0%)
No, *n* (%)	188 (56.5%)	160 (41.8%)	176 (62.0%)

Table 4. *Occurrence of more than one risk factor in the medical history of patients (n = 1000)*

Number of risk factors per patient	Number of patients, *n* (%)			
	Total number (*n* = 1,000)	Relief® Pro cream (*n* = 333)	Relief® Pro suppositories (*n* = 383)	Relief® Pro cream + suppositories (*n* = 284)
2	434 (43.4%)	153 (45.9%)	196 (51.2%)	85 (29.9%)
3	103 (10.3%)	13 (3.9%)	53 (13.8%)	37 (13%)
4	29 (2.9%)	2 (0.6%)	16 (4.2%)	11 (3.9%)
5	2 (0.2%)	0 (0%)	0 (0%)	2 (0.7%)
6	1 (0.1%)	1 (0.3%)	0 (0%)	0 (0%)

was selected in accordance with the approved instructions for medical use and taking into account the indications, as well as based on the personal preferences of the doctor or the preferences of the patient. The decision on the appointment of treatment was made before the patient was included in the study.

The study examined the indicators obtained by the doctor during the examination and interview of the patient at the visit, as well as those obtained from the patient's diaries: the dynamics of the severity of hemorrhoid symptoms on the Sodergren scale, the dynamics of the main symptoms of hemorrhoids (pain, bleeding, itching, edema, the presence of discharge, a feeling of discomfort) on the 4-point Likert scale (1 point — 'Absent', 2 points — 'Minimum', 3 points — 'Moderate' and 4 points — 'Very strong'), the change in the size of the largest hemorrhoid node compared to the initial values, the assessment of patient and researcher satisfaction with the treatment with the drug Relief® Pro, the severity of pain (VAS), the time of onset and duration of the analgesic effect after the first use of the drug. The consumer properties of both forms of the drug were also evaluated. The researchers also assessed the patients' adherence to recommendations to reduce the impact of risk factors (lifestyle changes, diet, etc.) and treatment.

Statistical Processing

Epidemiological statistical methods were used to analyze the data obtained. Interval (quantitative) data were described using: arithmetic mean, standard deviation, median, lower (25.0%) and upper (75.0%) quartiles, minimum, maximum and coefficient of variation.

To compare quantitative data distributed according to the normal distribution law, standard parametric criteria were used: Student's t-test for dependent/independent samples, analysis of variance (ANOVA) for independent samples.

To compare quantitative data distributed according to a law other than normal, standard nonparametric criteria were used: H-Kruskal-Wallis test, U-Mann-Whitney test, T-Wilcoxon test.

Table 5. *Some indicators of patients' lifestyle (n = 1000)*

Life style	The value of the indicator in different subgroups of treatment		
	Relief® Pro cream (*n* = 333)	Relief® Pro suppositories (*n* = 383)	Relief® Pro cream + suppositories (*n* = 284)
Eating habits (Fast food)			
Yes, *n* (%)	68 (20.4%)	99 (25.8%)	47 (16.5%)
No, *n* (%)	265 (79.6%)	284 (74.2%)	237 (83.5%)
Eating habits (Spicy food)			
Yes, *n* (%)	95 (28.5%)	147 (38,4%)	95 (33,5%)
No, *n* (%)	238 (71.5%)	236 (61.6%)	189 (66.5%)
Physical activity level			
Low, *n* (%)	93 (27.9%)	142 (37.1%)	48 (16.9%)
Average, *n* (%)	201 (60.4%)	204 (53.3%)	193 (68%)
High, *n* (%)	39 (11.7%)	37 (9.7%)	43 (15.1%)

Verification of compliance with the normal distribution law was carried out using the Shapiro-Wilk criterion. Multiple comparisons were carried out using the Benyamini-Yekutili correction.

RESULTS

Assessment of the Initial Data

The data obtained from the questionnaires made it possible to characterize the population of the patients with acute hemorrhoids according to such indicators as risk factors for the development of the disease and lifestyle.

It was found that the most common risk factors for the development of the disease were sedentary work (53.0%), constipation (47.6%), family history of disease (27.7%), as well as work associated with heavy physical exertion (18.0%). Risk factors such as obesity (7.6%), chronic diarrhea (0.6%), etc. (6.2%) were less common in the population. In the female population of the patients (*n* = 455), an anamnestic risk factor for hemorrhoids was additionally assessed, such as pregnancy (10.3%), childbirth (14.1%) and the postpartum period (4.4%).

In the study, it was possible to obtain data characterizing the patient population by the 'lifestyle' indicator (alcohol consumption, physical activity level, eating habits and frequency of meals). However, it was not possible to establish a relationship between lifestyle indicators and the outcome of treatment: the differences in the incidence of response distribution between the subgroups of the patients were random and were probably related to the individual characteristics of the patients.

During a local control, digital examination and instrumental confirmation of the diagnosis were carried out as part of routine coloproctological practice. According to the results of the digital examination (Table 6) at the inclusion visit, it was found that in the subgroups of the Relief® Pro cream and Relief® Pro cream + suppositories treatment, the largest hemorrhoid node was external — in 98.5% and 78.2% of the patients, respectively. At the same time, in 72.6% of patients from the Relief® Pro suppositories subgroup, the largest node was internal. It was found that the most frequent location of such nodes on the conventional clock face (regardless of shape) was localization at 3 o'clock (18.7% of patients), 7 o'clock (23.6% of patients) and 11 o'clock (15.7% of patients) of the conventional clock face, which is consistent with the literature data. The size of the largest hemorrhoid node before the treatment was 13.9 ± 4.7 mm in the Relief® Pro cream subgroup, 15.2 ± 5.2 mm in the Relief® Pro suppositories sub group, and 18.8 ± 5.5 mm in the Relief® Pro cream + suppositories subgroup. It is noteworthy that the size of the largest hemorrhoid node (average ± SD and median) in the Relief® Pro cream + suppositories treatment subgroup was significantly larger than in the other two groups.

According to the results of the digital examination, the initial severity of hemorrhoid symptoms such as edema and bleeding in the perianal area (in points on the Likert scale) averaged 2.8 ± 0.7 points (moderate) and 2.1 ± 0.8 points (minimum), respectively, in the population.

Table 6. *Finger examination data, initial data (n = 1000)*

Indicator	The value of the indicator in different subgroups of treatment		
	Relief® Pro cream (*n* = 333)	**Relief® Pro suppositories (*n* = 383)**	**Relief® Pro cream + suppositories (*n* = 284)**
Site of the largest hemorrhoid node			
Internal, *n* (%)	5 (1.5%)	278 (72.6%)	62 (21.8%)
External, *n* (%)	328 (98,5%) 328 (98.5%)	105 (27.4%)	222 (78.2%)
The size of the largest hemorrhoid node, mm			
Arithmetic mean	13.9 ± 4.7	15.2 ± 5.2	18.8 ± 5.5
Median	13	14	20
Minimum–Maximum	5–30	1–40	1–50
The severity of edema in the perianal area, distribution of responses on the Likert scale			
Absent, *n* (%)	35 (10.5%)	12 (3.1%)	15 (5.3%)
Minimum, *n* (%)	61 (18.3%)	47 (12.3%)	26 (9.2%)
Moderate, *n* (%)	222 (66.7%)	291 (76%)	197 (69,4%)
Very strong, *n* (%)	15 (4.5%)	33 (8.6%)	46 (16.2%)
The degree of bleeding in the perianal area, the istribution of responses on the Likert scale			
Absent, *n* (%)	129 (38.7%)	90 (23.5%)	96 (33.8%)
Minimum, *n* (%)	76 (22.8%)	130 (33.9%)	93 (32.7%)
Moderate, *n* (%)	128 (38.4%)	162 (42.3%)	94 (33.1%)
Very strong, *n* (%)	0 (0%)	1 (0.3%)	1 (0.4%)

According to the patients' diaries, the median pain at the start of the study in all subgroups of the treatment was 7 points (on a 10-point VAS scale). The severity of hemorrhoid symptoms before the start of the treatment on average in the population (in points on the Likert scale) was: bleeding — 2.2 ± 0.9 points (minimum), the severity of discharge — 2.2 ± 0.8 points (minimum), the severity of itching — 2.7 ± 0.7 points (moderate), the severity of edema — 2.9 ± 0.7 points (moderate), the severity of discomfort — 3.2 ± 0.5 points (moderate).

Individual data on the severity of the main symptoms of hemorrhoids assessed by the patient are presented in Table 7. According to these data, at the start of the study (Visit 1), the total amount of Sodergren scores in the Relief® Pro cream treatment subgroup was significantly lower compared to the other two subgroups ($p < 0.001$).

According to the information received from the study participants, some patients reported no bleeding, a significant part were the patients with minimal and moderate severity of bleeding (according to the Likert scale), in rare cases, the participants assessed the severity of their symptom as very strong (mainly in the Relief® Pro cream + suppositories subgroup). The median severity of bleeding before the start of the treatment was 3 points in the Relief® Pro suppositories subgroup and 2 points in the other two subgroups of the treatment.

The median severity of itching at the start of the study was 3 points on the Likert scale in all subgroups of the treatment. This symptom was present in the majority of the patients (91.0% in the Relief® Pro cream subgroup, 98.7% in the Relief® Pro suppositories subgroup, 78.2% in the Relief® Pro cream + suppositories subgroup). Moderate itching was most often detected in all subgroups of the treatment.

Moderate severity of edema was detected in the majority of the patients at the start of the study (more than 60% in the Relief® Pro cream subgroup, more than 70% in the Relief® Pro suppositories subgroup and more than 40% in the Relief® Pro cream + suppositories subgroup). For the patients with very pronounced edema, the combined treatment was prescribed most often (about 40% of the patients) in the Relief® Pro cream + suppositories subgroup.

The median indicator of the abundance of discharge before the start of the treatment was 3 points on the Likert scale in the Relief® Pro suppositories subgroup and 2 points in the other two

Table 7. *Dynamics of assessing the severity of hemorrhoidal disease on the Sodergren scale: data obtained during a standardized patient survey*

Indicator	The total amount of points on the Sodergren scale			Change relative to the baseline	
	Visit 1 (Day 1)	Visit 2 (Day 5–7)	Visit 3 (Day 10–14)	Visit 2 — Visit 1	Visit 3 — Visit 1
Relief® Pro cream (*n* = 333)					
N	333	332	312	332	312
Mean ± SD	**3.74 ± 3.19**	**0.50 ± 1.40**	**0.05 ± 0.47**	–3.24 ± 3.16	–3.60 ± 3.10
Relief® Pro suppositories (*n* = 383)					
N	383	383	379	383	379
Среднее ± SD Mean ± SD	**5.05 ± 3.23**	**0.53 ± 1.31**	**0.05 ± 0.46**	–4.53 ± 3.23	–4.97 ± 3.13
Relief® Pro cream + suppositories (*n* = 284)					
N	284	284	263	284	263
Mean ± SD	**5.53 ± 3.12**	**1.67 ± 2.07**	**0.22 ± 1.13**	–3.86 ± 2.85	–4.86 ± 2.70

subgroups of the treatment. In most patients, in their opinion, the severity of the symptom was moderate, minimal, or the symptom was absent.

The overwhelming majority of the patients regarded the severity of discomfort as moderate or very severe.

The greatest feeling of discomfort at the beginning of the study was experienced by the patients from the Relief® Pro cream + suppositories subgroup (4 points on the Likert scale compared to 3 points in the other two subgroups of the treatment).

In addition to the local treatment of hemorrhoids with Relief® Pro, half of the patients (49.7%) used concomitant treatment. At the same time, bioflavonoids were among the most commonly taken drugs. So, drugs of this group were taken by: 120 (36.0%) patients of the Relief® Pro cream subgroup; 137 patients (35.8%) of the Relief® Pro suppositories subgroup, and 194 patients (68.3%) of the Relief® Pro cream + suppositories subgroup. Laxatives and proton pump inhibitors are also commonly taken medications. It is obvious that the main amount of drugs was taken by the patients or recommended by a doctor in connection with the underlying disease.

Assessment of the Treatment Effectiveness

The effectiveness of the studied treatment was evaluated in all the patients who used the Relief® Pro during the study at least once. Already by the second visit (day 5–7) in all the treatment subgroups, according to the patients' estimates, there was a significant change in the severity of hemorrhoidal disease on the Sodergren scale compared to the initial values and remained until the end of observation ($p < 0.001$). Thus, the average change in the indicator of the total sum of Sodergren scores relative to the the baseline level in the Relief® Pro cream treatment subgroup was: — 3.24 ± 3.16 at Visit 2 and — 3.60 ± 3.10 at Visit 3; in the Relief® Pro suppositories subgroup — 4.53 ± 3.23 and — 4.97 ± 3.13 at Visit 3; in the Relief® Pro cream + suppositories subgroup — 3.86 ± 2.85 at Visit 2 and — 4.86 ± 2.70 at Visit 3 (Table 7).

It is noteworthy that the intergroup differences in the value of this indicator, which occurred before the start of the treatment with the studied drug, were also manifested at observation Visits 2 and 3. In this regard, it was assumed that the differences are due to the form and degree of hemorrhoids, as well as the individual characteristics of the patients included in the study. At the same time, despite the detected intergroup differences, in all the subgroups of the treatment, there was a positive change of a decrease in the severity of hemorrhoids on the Sodergren scale, compared with the initial values.

According to the patients' estimates, the use of the studied drug Relief® Pro, regardless of the dosage form, led to a significant decrease in the severity or disappearance of the main symptoms of hemorrhoids — bleeding, itching, edema, the presence of discharge, discomfort by Visit 2 and in almost all the patients — by the end of observation at visit 3 (Fig. 1–3). The assessment of symptoms in points was — at Visit 2: discomfort 2.2 ± 0.6 points, edema 2.1 ± 0.7 points, itching 1.9 ± 0.6

points, the presence of discharge 1.5 ± 0.6, bleeding 1.5 ± 0.6 points on the Likert scale; assessment at Visit 3: discomfort 1.4 ± 0.6 points, edema 1.3 ± 0.5 points, itching 1.2 ± 0.4 points, the presence of discharge 1.0 ± 0.2 points, bleeding 1.0 ± 0.2 points on the Likert scale.

A similar pattern was observed with respect to the symptoms assessed by the medical researcher during the digital examination: these symptoms disappeared or their intensity was minimized in most patients by Visit 2 (on average, in the population, edema in the perianal area — 82.3%, bleeding — 98.3%) and in almost all the patients — by Visit 3 (edema in the perianal area — 98.4%, bleeding — 99.8%). At Visit 2, the severity of edema in the perianal area was 2 ± 0.6 points on the Likert scale (minimum), at Visit 3–1.2 ± 0.5 points (absent); the severity of bleeding at Visit 2 was 1.4 ± 0.5 points (absent or minimum), at Visit 3–1.0 ± 0.2 points (absent) (the data are presented for the general population) (Figure 2, 3).

The presented data demonstrate that in all the subgroups of the treatment, without exception, there was a positive trend in the severity of all the assessed symptoms.

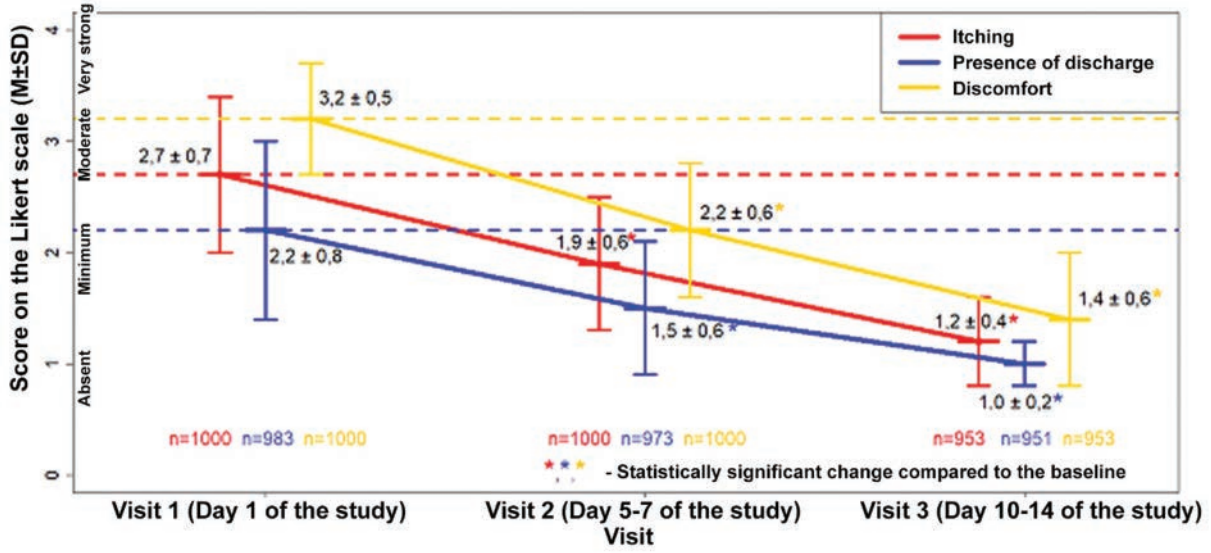


Figure 1. *Dynamics of the severity of the main symptoms of hemorrhoids: Itching, the presence of discharge, Discomfort, according to the patient's assessment (n = 1000)*

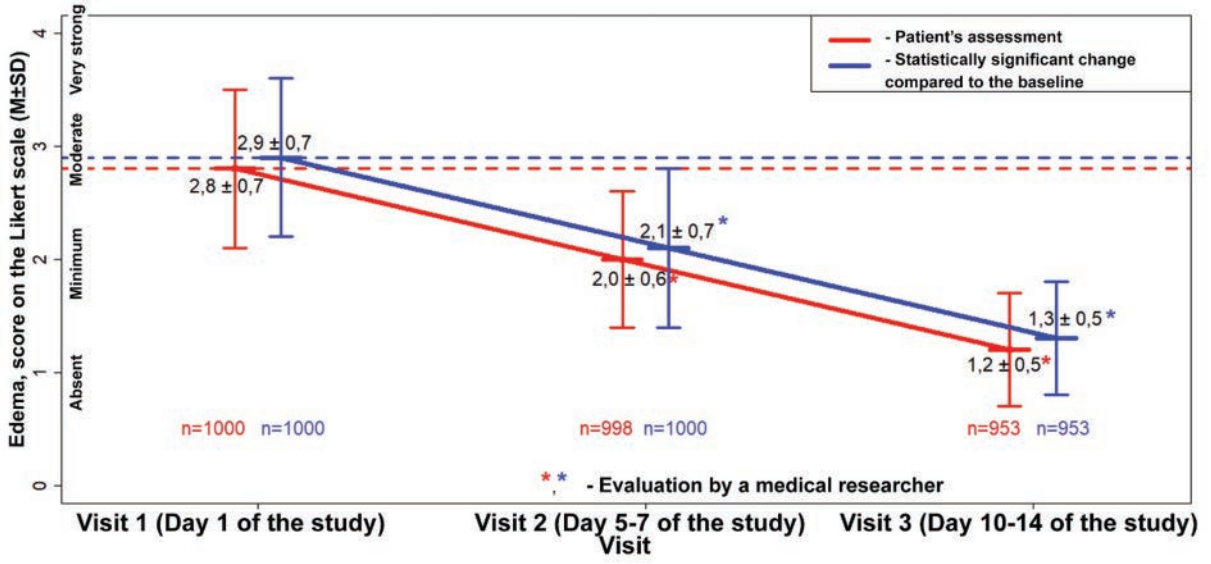


Figure 2. *Dynamics of symptom severity* ***Edema in the perianal region*** *according to the doctor's and patient's estimates (n = 1000)*

Table 8. *Dynamics of symptom severity* ***Edema in the perianal region*** *which was evaluated during the finger examination*

Indicator	Edema in the perianal area, score on the Likert scale[1]			Change relative to the baseline	
	Visit 1 (Day 1)	Visit 2 (Day 5–7)	Visit 3 (Day 10–14)	Visit 2 — Visit 1	Visit 3 — Visit 1
Relief® Pro cream (*n* = 333)					
N	333	331	311	331	311
M ± SD	2.65 ± 0.73	1.86 ± 0.55	1.10 ± 0.32	–0.80 ± 0.60	–1.57 ± 0.73
Relief® Pro suppositories (*n* = 383)					
N	383	383	379	383	379
M ± SD	2.90 ± 0.57	2.04 ± 0.49	1.21 ± 0.42	–0.86 ± 0.45	–1.69 ± 0.61
Relief® Pro cream + suppositories (*n* = 284)					
N	284	284	263	284	263
M ± SD	2.97 ± 0.68	2.20 ± 0.69	1.47 ± 0.59	–0.76 ± 0.54	–1.50 ± 0.67

Changes in the Size of the Largest Hemorrhoid Node

Against the background of the use of the drug Relief® Pro in all the subgroups of the treatment, there was a decrease in the size of the largest hemorrhoid node ($p < 0.001$) (Table 10). At the same time, the results obtained indicate the effectiveness of the treatment regardless of the dosage form of the drug used and the form of hemorrhoids — both external and internal nodes decreased.

The most significant decrease in this indicator (in percent) occurred in the Relief® Pro cream and the Relief® Pro suppositories subgroups — by 41.72% and 36.84% on day 5–7 of the treatment and by 76.98% and 69.08% on day 10–14, respectively. Nevertheless, in the combined treatment group, the results were also impressive: the reduction in the size of the largest node was 26.06% and 51.6% at visits 2 and 3, respectively. These data suggested that the differences are due to the form and degree of hemorrhoids, as well as the individual characteristics of the patients included in the study.

Assessment of Analgesic Effect

During the study, the patients were asked to fill out a one-page diary at home in order to assess the rate of onset and severity of the analgesic effect after the first use of the studied drug. On the reduction of the severity of pain syndrome after the first use of the Relief®, reported a total of about 95% of the patients: 98.5%, 98.7%, and 88.7% of the patients receiving the Relief® Pro cream, suppositories or a combination thereof, respectively. At the same time, in the group that received the

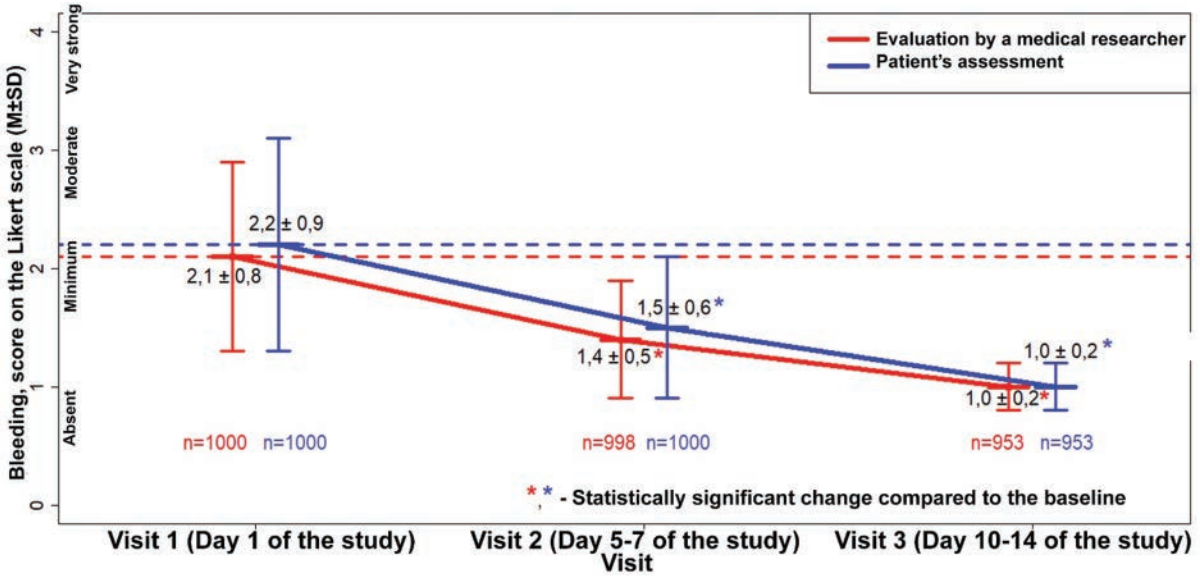


Figure 3. *Dynamics of symptom severity* ***Bleeding*** *according to the estimates of the doctor and the patient (n = 1000)*

Table 9. *Dynamics of symptom severity* ***Bleeding in the perianal area*** *which was evaluated during the finger examination*

Indicator	Bleeding in the perianal area, score on the Likert scale[1]			Change relative to the baseline	
	Visit 1 (Day 1)	Visit 2 (Day 5–7)	Visit 3 (Day 10–14)	Visit 2 — Visit 1	Visit 3 — Visit 1
Relief® Pro cream (*n* = 333)					
N	333	331	311	331	311
Average ± SD	2.0 ± 0.88	1.38 ± 0.51	1.02 ± 0.15	–0.63 ± 0.67	–1.04 ± 0.88
Relief® Pro suppositories (*n* = 383)					
N	383	383	379	383	379
Average ± SD	2.19 ± 0.80	1.44 ± 0.53	1.02 ± 0.16	–0.75 ± 0.63	–1.18 ± 0.8
Relief® Pro cream + suppositories (*n* = 284)					
N	284	284	263	284	263
Average ± SD	2 ± 0.83	1.47 ± 0.55	1.04 ± 0.2	–0.53 ± 0.61	–1.00 ± 0.81

Table 10. *Dynamics of changes in the size of the largest hemorrhoid node (n = 1000)*

Indicator	The size of the largest hemorrhoid node, mm			Change relative to the baseline	
	Visit 1 (Day 1)	Visit 2 (Day 5–7)	Visit 3 (Day 10–14)	Visit 2 — Visit 1	Visit 3 — Visit 1
Relief® Pro cream (*n* = 333)					
N	333	329	308	329	308
M ± SD	13.9 ± 4.7	7.9 ± 4.4	3.1 ± 4.1	–5.8 ± 2.6	–10.7 ± 3.2
Relief® Pro suppositories (*n* = 383)					
N	383	383	379	383	379
M ± SD	15.2 ± 5.2	9.5 ± 4.9	4.6 ± 4.9	–5.6 ± 2.3	–10.5 ± 3.4
Relief® Pro cream + suppositories (*n* = 284)					
N	284	284	n = 263	284	263
M ± SD	18.8 ± 5.5	13.9 ± 4.9	8.9 ± 4.5	–4.9 ± 2.8	–9.7 ± 4.5

Relief® Pro as part of a combination of the dosage forms, the least number of the patients reported such a decrease ($p < 0.001$). This fact was probably due to the combined form of the disease, as well as the severity, which was slightly higher in this subgroup.

Initially, the severity of pain on the VAS scale before the first use of the drug was higher in the Relief® Pro suppositories subgroup: 7.47 ± 1.35 points *vs* 6.85 ± 1.50 points (Relief® Pro cream) and 6.81 ± 1.73 points (Relief® Procream + suppositories) ($p < 0.001$). At the same time, a decrease in the severity of pain after the first use of the drug Relief® Pro was the highest ($p < 0.001$) in the Relief® Pro cream + suppositories treatment subgroup: — 4.86 ± 2.15 points, compared with — 3.14 ± 1.45 points and — 3.16 ± 1.74 points in the Relief® Pro cream and the Relief® Pro suppositories subgroups, respectively.

The rate of onset of the maximal analgesic effect after the first use of the drug was the lowest in the Relief® Pro cream + suppositories subgroup: 39.83 ± 25.26 min. ($p < 0.001$), *vs* with 20.19 ± 16.37 min. in the Relief® Pro cream subgroup and 16.98 ± 11.12 min. in the Relief® Pro suppositories subgroup.

The duration of the analgesic effect of the drug in the Relief® Pro cream + suppositories subgroup was also the smallest: 130.99 ± 71.57 min. ($p < 0.001$) compared to 198.84 ± 92.19 min. and 188.25 ± 93.74 min. in the Relief® Pro cream and the Relief® Pro suppositories subgroups, respectively (Table 11).

At the same time, when assessing the severity of pain sensations at Visits 1, 2 and 3, there was a pronounced change with a significant decrease in indicators at Visit 2 compared to the initial and minimum values or the absence of pain at Visit 3 in all the subgroups of the treatment (Table 12).

Identified in the Relief® Pro cream + suppositories subgroup, differences in reducing the severity of pain (both during the first use of the drug and according to the results of the course of the treatment), the rate of onset of the maximum analgesic effect and the duration of the analgesic effect are probably due to several factors: the combined form of hemorrhoids and the more pronounced severity of the disease in this subgroup, as well

as the need to use two dosage forms of the drug under study simultaneously.

Assessment of Treatment Satisfaction, Compliance to Recommendations and Treatment

Both the patients and the doctors noted very high satisfaction with the results of the treatment with the Relief® Pro drug. By the end of the course of the treatment, on average, in about 97% of the cases, the research doctors were satisfied with the results of the treatment: 99.1% of the cases in the Relief® Pro cream subgroup; 99.5% of the cases in the Relief® Pro suppositories subgroup; 92.8% of the cases in the Relief® Pro cream + suppositories subgroup.

The vast majority of the patients, on average about 96%, were also satisfied with the studied treatment at the end of the treatment: 98.7% of the cases in the Relief® Pro cream subgroup; 98.7% of the cases in the Relief® Pro suppositories subgroup; 90.5% of the cases in the Relief® Pro cream + suppositories subgroup.

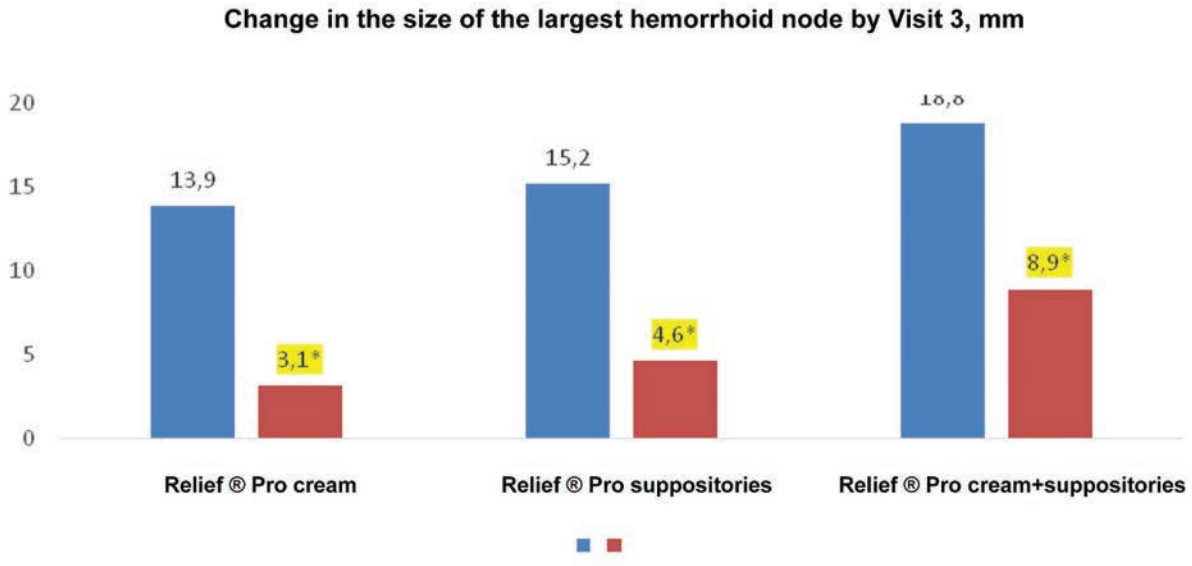
The conducted research allowed to obtain data from real clinical practice on patients' adherence to such recommendations of a research doctor as compliance with hygiene rules, diet, recommendations regarding physical activity, the use of dietary supplements, the use of concomitant treatment drugs. The vast majority of the patients (more than 99%), regardless of the subgroup of the treatment, fully or partially followed the recommendations of the researcher on hygiene, more than 97% of the patients (fully or partially) followed the diet, more than 96% of the patients followed the recommendations on physical activity. Recommendations for the use of dietary supplements were provided to the patients in total in more than 70% of the cases, while most of the patients (more than 70%) either fully or partially followed these recommendations. It is worth noting that only about half of the patients from the Relief® Pro cream + suppositories subgroup received recommendations for the use of dietary supplements.

The overwhelming majority of the patients (more than 81%) also followed the recommendations of the research doctor regarding the intake of other medications, concomitant treatment drugs.

Most of the patients followed the prescriptions of the research doctor regarding the dosage form and the frequency of the use of the Relief® Pro drug. The average duration of the use of the Relief® Pro drug by the patients was:

- 11.4 ± 1.9 days (Relief® Pro cream),
- 11.4 ± 1.7 days (Relief® Pro suppositories),
- 12.6 ± 1.4 days (Relief® Pro cream + suppositories);

The duration of the use of the drug in the Relief® Pro cream + suppositories subgroup was the highest ($p < 0.001$). This difference may probably be



** statistically significant differences compared to the initial data ($p < 0.001$)*

Figure 4. *The size of the largest hemorrhoid node during the treatment with Relief® Pro*

Table 11. *Dynamics of changes in the severity of pain during the first use of the drug (n = 1000)*

Groups	The severity of pain before using the drug, the score on the VAS scale	The maximum degree of pain reduction after the first use of the drug, the score on the VAS scale	The onset of the maximum analgesic effect after the 1st use, min.	Duration of analgesic effect, min.
Relief® Pro cream (*n* = 333)	6.85 ± 1.50	–3.14 ± 1.45	20.19 ± 16.37	198.84 ± 92.19
Relief® Pro suppositories (*n* = 383)	7.47 ± 1.35	–3.16 ± 1.74	16.98 ± 11.12	188.25 ± 93.74
Relief® Pro cream + suppositories(*n* = 284)	6.81 ± 1.73	–4.86 ± 2.15	39.83 ± 25.26	130.99 ± 71.57

Table 12. *The severity of pain during the treatment (n = 1000)*

Indicator	Pain, score on the VAS scale			Change relative to the baseline	
	Visit 1 (Day 1)	Visit 2 (Day 5–7)	Visit 3 (Day 10–14)	Visit 2 — Visit 1	Visit 3 — Visit 1
Relief® Pro cream (*n* = 333)					
N	333	333	310	333	310
M ± SD	6.79 ± 1.64	3.04 ± 1.47	0.65 ± 1.06	–3.75 ± 1.44	–6.27 ± 1.83
Median	7	3	0	–4	–7
Relief® Pro suppositories (*n* = 383)					
N	383	383	380	383	380
M ± SD	7 ± 1.43	3.50 ± 1.59	1.02 ± 1.5	–3.5 ± 1.51	–5.98 ± 1.89
Median	7	3	0	–4	–6
Relief® Pro cream + suppositories(*n* = 284)					
N	284	284	263	284	263
M ± SD	6.85 ± 1.81	4.46 ± 1.99	2.57 ± 1.78	–2.39 ± 1.46	–4.22 ± 1.6
Median	7	5	2	-2	-4

due to the slower dynamics of changes in the severity of hemorrhoidal disease, measured by the patients on the Sodergren scale, in this subgroup of the treatment.

Adverse Events (Safety/Tolerability)

During the follow-up, a total of 5 adverse events were registered in 3 patients: 2 adverse events (AE) in 1 patient in the Relief® Pro cream treatment subgroup and 3 AEs in 2 patients in the Relief® Pro suppositories subgroup.

Edema of the perianal area (3 cases) and bleeding in the perianal area (2 cases) were recorded. No cases of AE in the patients in the Relief® Pro cream + suppositories subgroup were identified.

All the AEs were regarded by the researcher as unrelated to the drug used. All the AEs registered during the study were resolved by the end of the study.

No cases of serious adverse events (SAE) were detected during this study.

DISCUSSION

Hemorrhoids are an urgent and widespread problem of modern man, which brings discomfort and great inconvenience to daily activity. Hemorrhoids are increasingly affecting people of young working age [2]. Inactive/sedentary lifestyle and other factors contributing to stagnation of blood circulation in the pelvic organs, and primarily in the rectum, as well as errors in nutrition and unstable bowel function lead to the emergence of a disease or exacerbation of an already existing process.

Topical symptomatic agents are an integral component of the complex conservative treatment of hemorrhoids. Increasingly, combined drugs that affect several symptoms at the same time are being used. In addition, combined drugs help to increase compliance and facilitate patients' compliance with the treatment regimen. The combination of topical GCS fluocortolone pivalate and the local anesthetic lidocaine has been successfully

used for many years and has been studied in several studies [15–17].

However, data on the efficacy and tolerability of the drug in real clinical practice have not been available to date.

The purpose of this prospective, multicenter observational study was to assess the efficacy and safety of treatment with Relief® Pro in patients with acute hemorrhoids of the I–II stages and exacerbation of chronic hemorrhoids.

In the study, in real conditions, positive changes were noted in patients with hemorrhoids with respect to the severity of the disease on the Sodergren scale, the severity of hemorrhoid symptoms and changes in the size of the largest hemorrhoid node. So, against the background of the use of the studied drug Relief® Pro regardless of the dosage form, already at the second visit, 5–7 days after the start of the treatment, the main symptoms of hemorrhoids — bleeding, itching, edema, the presence of discharge, discomfort — significantly decreased or disappeared, and were absent in almost all the patients by the end of the observation. Against the background of the treatment with the studied drug, the size of the largest hemorrhoid node by the end of the study decreased by 76.9% in the group of the patients who were prescribed the Relief® Pro cream, by 69.1% in the group of the patients treated with the Relief® Pro suppositories, and by 51.6% in the group of the patients treated with the both forms of the drug.

At the same time, the results obtained indicate the effectiveness of the treatment regardless of the dosage form of the drug used and the form of hemorrhoids — both external and internal nodes decreased. The pronounced effect of the drug on the pain syndrome, the rate of development and duration of the analgesic effect was noted.

The number of the patients with acute hemorrhoids of the I stage, II stage and exacerbation of chronic hemorrhoids in the study was approximately the same. However, the distribution of the patients by the subgroups of the treatment was uneven, since it was based on the type of dosage form of the prescribed treatment (cream, suppositories or a combination thereof). It can be assumed that the prescription of a particular dosage form of the Relief® Pro drug was carried out basing on the form of the disease: treatment of the external form of hemorrhoids was more often carried out with the cream (n = 318, 62%); the internal ones — with the suppositories (n = 253, 89.7%); and the combined form — with a combination of dosage forms of the cream + suppositories (n = 123, 60%).

It turned out that in the subgroup of the treatment with the use of the Relief® Pro cream and suppositories, the proportion of the patients with the 2nd degree hemorrhoids and with combined hemorrhoids (internal + external) was higher in comparison with the other subgroups, which could affect the treatment effectiveness (reducing the symptoms severity) obtained during the treatment. At the same time, despite the detected intergroup differences, in all the treatment subgroups, without exception, there was a positive change in all the efficiency indicators recorded by the researcher.

The initial characteristics of the patients included in this study are consistent with the data on the population of patients with hemorrhoids. These are people of active working age, who have several risk factors/triggers of hemorrhoids. It was noted that the overwhelming number of the patients followed the doctor's recommendations on the treatment duration with the Relief® Pro drug, as well as on compliance with diet, hygiene rules, and physical activity.

It seems important that both the patients and the doctors were very satisfied with the treatment results with the Relief® Pro drug.

Good tolerability of the treatment was recorded — adverse events were isolated and were not associated with the use of the drug under study.

Several limitations of this study also need to be taken into account. Since the study was observational and did not include a control group, it was impossible to conduct a direct assessment of the effectiveness of the Relief® Pro drug. Due to the open study design, a potential systematic evaluation error may be detected.

In addition, standard clinical conditions implied the impossibility of monitoring the use of concomitant treatment and the inability to obtain data at all time points, which could negatively affect the interpretation of the data.

CONCLUSION

The results of the study confirmed the efficacy and safety of the studied Relief® Pro drug when using it in patients with acute hemorrhoids of the 1–2 degrees and exacerbation of chronic hemorrhoids. Against the background of the use of the drug in the form of cream, suppositories or a combination of them, the severity of hemorrhoidal disease, the severity of the main symptoms of the disease and the size of hemorrhoids decreased significantly and in a short time. Monitoring of the safety of medical use of the drug confirmed its good tolerability and the absence of influence on vital functions.

In the study, valuable data were obtained characterizing the patient population, approaches to the diagnosis and treatment of hemorrhoids in real clinical practice. Besides, additional information was obtained on patients' adherence to the doctor's recommendations, patient and researcher's satisfaction with the treatment, as well as an assessment of patients' preferences regarding the dosage form of the drug under study and its consumer properties was made.

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