THE EFFICACY AND TOLERABILITY OF AVARICON® HEMOR MEDICAL PREPARATION IN THE TREATMENT OF HEMORRHOIDS COMPARED TO PLACEBO – A PROSPECTIVE DOUBLE BLIND RANDOMIZED CLINICAL STUDY

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Summary
Introduction. Despite the high incidence of hemorrhoidal disease and the widespread use of numerous topical preparations, there is still a lack of information regarding their efficacy. Therefore, the aim of this study was to assess the efficacy and tolerability of a new topical medical preparation containing sodium hyaluronate, calendula extract, hamamelis extract and mentha piperita essential oil as major components.

Material and Methods. This prospective double-blind randomized clinical study included 49 patients with a diagnosis of hemorrhoidal disease. The patients were randomly assigned to two groups: Avaricon® group that included patients who applied 0.20% Avaricon® Hemor and a placebo group who applied placebo during 2 weeks. The effects of Avaricon® Hemor on the symptoms of hemorrhoidal disease, its safety, tolerability as well as compliance and adherence of study patients were analyzed.

Results. Our results showed that Avaricon® Hemor was significantly superior to placebo in controlling most symptoms of hemorrhoidal disease.

Conclusion. The tested medical agent showed to be effective with good tolerability and safety profile indicating its possible use in various therapeutic protocols in the management of hemorrhoidal disease.

Key words: Hemorrhoids; Treatment Outcome; Administration, Topical; Hyaluronic Acid; Drug Tolerance; Patient Compliance; Medication Adherence

Sažetak
Uvod. Uprkos velikoj učestalosti hemoroidne bolesti i širokoj upotrebi brojnih aktuelnih preparata, još uvek nedostaju informacije o njihovoj efikasnosti. Stoga je cilj naše studije bio da se proceni efikasnost i podnošljivost novog medicinskog proizvoda koji sadrži natrijum-hijaluronat, ekstrakt nevena, ekstrakt hamamelisa i esencijalno ulje nane kao glavne komponente. Materijal i metode. Ovo je bila dvostruko slepa randomizirana prospektivna klinička studija koja je obuhvatila 49 pacijenata sa dijagnostikovanom hemoroidnom bolešću. Pacijenti su nasumično svrstani u dve grupe: Avaricon® grupa koja je uključivala pacijente koji su primenjivali 0,20% Avaricon® Hemor i placebo grupa koji je primenjivala placebo dve nedelje. Zabeleženi su efekti medicinskog sredstva Avaricon® Hemor na simptome hemoroidne bolesti, bezbednost, podnošljivost i komplijansu i adherenciju pacijenata.

Rezultati. Naši rezultati su pokazali da je medicinski uređaj Avaricon® Hemor bio značajno superiorniji od placebo u kontroli većine simptoma hemoroidne bolesti. Zaključak. Ispitivani medicinski uređaj je efikasan sa dobrom podnošljivću i bezbednosnim profilom što ukazuje na njegovu moguću primenu u različitim terapijskim protokolima za lečenje hemoroidne bolesti.

Ključne reči: hemoroidi; ishod lečenja; topikalna primena; hijaluronska kiselina; tolerancija na lekove; komplijansa; adherencija

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Abbreviations
HA – hyaluronic acid  
SH – sodium hyaluronate  
CE – Calendula extract  
HE – Hamamelis extract  
MPO – essential oil from Mentha piperita  
VAS – visual analogue scale  
MMAS – Morisky medication adherence scale  
SD – standard deviation  
SEM – standard error of the mean

Introduction

Hemorrhoidal disease is one of the most common anorectal conditions which affects up to one quarter of adults worldwide [1, 2]. It is characterized by clusters of vascular tissues, smooth muscles and connective tissues which occur due to abnormal dilatation of the vascular channel and pathological changes within the anal cushions [3, 4]. Although the etiology underlying the development of hemorrhoids has not been completely elucidated, increased intra-abdominal pressure during pregnancy or straining may be the cause venous engorgement of the hemorrhoidal plexus [5, 6]. Patients who suffer from hemorrhoids experience bleeding, fecal soiling, pruritus etc., which strongly affects their quality of life [7]. While internal hemorrhoids are often painless, external hemorrhoids are associated with significant pain and discomfort due to activation of peri-anal innervations associated with thrombosis [3, 5].

Numerous surgical and nonsurgical strategies have been proposed for the management of hemorrhoidal disease with the aim to relieve the symptoms of hemorrhoids rather than to cure them [3, 4]. Additionally, medical approach depends on the type and severity of hemorrhoids; topical and systemic drugs can be applied in grade 1 and grade 2 hemorrhoids, while surgical procedures are required in more severe cases [4, 8]. Topical preparations involve creams, gels and suppositories usually containing local anesthetics, corticosteroids, lubricants and or anti-inflammatory agents which provide temporary symptomatic relief [1, 9–11]. Nevertheless, true benefits of these preparations are still lacking, indicating a need to test the effectiveness of numerous available, as well as novel formulations, in randomized clinical trials [4, 8]. Few papers have addressed the encouraging potentials of hyaluronic acid (HA) that promotes extracellular matrix remodeling [1, 12]. Protective effects of topical formulations used for hemorrhoids may be achieved by adding components of plant origin together with HA. However, results in this field still need to be examined [12].

Regarding all the above mentioned, the aim of our study was to assess the efficacy and tolerability of a new topical medical preparation containing sodium hyaluronate (SH), calendula extract (CE), hamamelis extract (HE) and mentha piperita essential oil (MPO) as major ingredients.

Material and Methods

This study was designed as a randomized, double-blind, parallel group, placebo-controlled mono-center trial. It was conducted at the Clinic of Gastroenterology, Clinical Center of Kragujevac, Serbia, from January to April 2019.

The study protocol was approved by the Ethics Committee of the Clinical Center of Kragujevac and it was carried out according to the Declaration of Helsinki, Good Clinical Practice and International Conference on Harmonization guidelines. All the participants were informed about the research protocol before giving their written consent to participate in the study.

The study included 49 patients with a diagnosis of hemorrhoidal disease that were randomly assigned to two groups:

- **Avaricon® group - patients (n = 19) who applied 0.20% Avaricon® Hemor at the affected site according to the manufacturer’s instructions, 2 or 3 times daily for 14 days**
  - Placebo group - patients (n = 30) who applied placebo in the same manner.
- **Avaricon® Hemor and placebo were applied at a dose of 0.5 to 1 g corresponding to a quantity of 1 to 2 cm of cream [12].**

The inclusion criteria were: both genders, informed written consent from each participant, age over 18 years, and diagnosis of grades I–III hemorrhoids according to the international classification. The exclusion criteria were: suspected hypersensitivity and/or contraindications to active components or excipients of the examined product, breast feeding, oocyte donation or implantation during the study period, patients who cannot follow the investigation due to language comprehension problems, speech impediment, medical intervention or state that may interfere with the study protocol, patients who were included in another clinical trial at least 30 days before the beginning of the current study, patients subjected to surgical interventions of the anal region in the last 30 days, presence of inflammatory disease or other diseases of the gastrointestinal system [12]. Each participant could leave the clinical study at any time for any reason without consequences. All patients who met the inclusion criteria were enrolled in the investigations. Participants were subjected to clinical evaluation and examination by a gastroenterologist one day before the beginning of the study (baseline) and after completion of the 14-day treatment (14th day) (Scheme 1).

![Scheme 1. Study flow diagram](image-url)
**Assessment of the Avaricon® Hemor efficacy**

In order to determine the efficiency of Avaricon® Hemor, the following parameters were recorded at the beginning (baseline) and at the end of the treatment (14th day): anal pain intensity, pain during defecation, bleeding self-evaluation, and assessment of the grade of hemorrhoidal disease.

**Visual analog scale for the efficacy assessment of Avaricon® Hemor**

The visual analog scales (VAS) is a numerical self-evaluation scale (0 – 100) where zero means absence of symptoms, and 100 mm corresponds to severe symptoms [12]. The following parameters were assessed by VAS: intensity of anal pain, intensity of anal pain during defecation, and intensity of anal bleeding.

**Assessment of the safety and tolerability of Avaricon® Hemor**

The safety and tolerability of the examined medical preparation was evaluated by a physician and by self-reporting unspecific and specific adverse effects. Tolerability was measured on a 4-point scale: 1 (“very good”), 2 (“good”), 3 (“poor”) and 4 (“very poor”) after 14th day of treatment and 7 days after treatment cessation. Additionally, at the same time, a 3-point descriptive scale: 1 (“better”), 2 (“no change”) and 3 (“worse”) was used for global assessment of improvement of the disease [12].

**Compliance of the study population assessment**

Direct and indirect methods were used for the assessment of compliance after 7 and 14 days of treatment. These procedures included self-reports about the amount of residual test substance, direct medical checking of the residual test substance, patients’ statements regarding the applied dose, as well as the time and route of administration during the study protocol [15].

**Assessment of the study population adherence**

Adherence was assessed via medication event monitoring system (MEMS) and Morisky mediation adherence scale (MMAS) after the treatment. The MMAS consists of four yes/no questions “Do you ever forget to take your medication?”; “Do you take care about the time when you should take the medication?”; “If you feel better, do you sometimes skip taking your medication?”; and “Do you stop taking your medication if you feel worse?” The total score varies from 0 to 4; 0 corresponds to high degree of adherence, 1 – 2 to moderate adherence, and 3 – 4 to low degree of adherence [14].

**Used medications**

Avaricon® Hemor cream (20 g tube with applicator) is a certified product of Pharmanova (Belgrade, Serbia) pharmaceutical company that contains purified water, poloxamer 407, macrogol 400, liquid paraffin, Calendula officinalis flower liquid extract, ethanol, dexamethasone, Hamamelis virginiana leaf dry extract, disodium phosphate dodecahydrate, mentha piperita essential oil, allantoin, sodium hyaluronate, sodium dihydrogen phosphate dihydrate, and chlorhexidine digluconate. The placebo contained Vaseline and color which made the formulation indistinguishable from Avaricon® Hemor cream.

Statistical analysis was performed using Statistical Package for the Social Sciences, 20.0 version for Windows. Descriptive statistics were used to calculate arithmetic mean with dispersion measures – standard deviation (SD) and standard error of the mean (SEM). Values were expressed as mean ± SEM. Distribution of data was checked by Shapiro – Wilk test and Mann – Whitney test; Chi squared test and Pearson coefficient were used for data analysis. Values of p < 0.05 were considered to be statistically significant, while p < 0.01 were highly statistically significant.

**Table 1. Patient baseline descriptive characteristics**

|                         | Avaricon® group | Placebo group | p    | p    |
|-------------------------|-----------------|---------------|------|------|
| **Gender/Pol**          |                 |               |      |      |
| Male/Muški, n (%)       | 10 (52.6)       | 19 (63.3)     | > 0.05 |      |
| Female/Zenski, n (%)    | 9 (47.4)        | 11 (36.7)     | > 0.05 |      |
| **Age (mean ± SEM)/Starost (sredina ± SEM)** | 52.32 ± 2.5 | 45.87 ± 2.2 | > 0.05 |      |
| **Diagnosis/Dijagnoza** |                 |               |      |      |
| External hemorrhoids, n (%) | 12 (63.16) | 7 (23.33)     | < 0.05 |      |
| Internal hemorrhoids, n (%) | 7 (36.84)  | 23 (76.67)   | < 0.05 |      |
| **Duration of disease (mean ± SEM)/Trajanje bolesti (sredina ± SEM)** | 39.68 ± 8.07 | 34.60 ± 6.99 | > 0.05 |      |

**Results**

**General characteristics of the study population**

Baseline clinical and demographic characteristics of the patients enrolled in the research are presented in **Table 1**. There was no difference between groups, except in the frequency of diagnosis (p < 0.05).

**The effects of Avaricon® Hemor on the hemorrhoid symptoms after a 14-day treatment compared with the placebo**

A significant drop in the number of patients with anal pain was found both after the application of Avaricon® Hemor cream and placebo (p < 0.05). At the beginning of the study and prior to treatment, the intensity of pain was statistically significantly higher in the Avaricon® group (p < 0.05). However, at the end of 14-day Avaricon® Hemor cream treatment, there was a decrease in anal pain intensity compared to...
Table 2. Assessment of disease severity and incidence of hemorrhoid symptoms

| Table 2. Skala za procenu težine bolesti i prisustva simptoma hemoroida |
|---------------------------------------------------------------|
| Avaricon® group/Avaricon® grupa/Placebo group/Placebo grupa | Baseline Početne vrednosti | After 14 day Nakon 14 dana | Baseline Početne vrednosti | After 14 day Nakon 14 dana |
| Anal pain/Bol analne regije, n (%) | 13 (68.42) | 11 (57.89)* | 23 (76.66) | 21 (70)* |
| No anal pain/Odsustvo bola analne regije, n (%) | 6 (31.58) | 8 (42.11)* | 7 (23.33) | 9 (30)* |
| Anal pain intensity 1-10 (mean ± SEM) | 4.74 ± 0.63 | 2 ± 0.29** | 3.57 ± 0.29* | 2.57 ± 0.23* |
| Intenzitet bola analne regije 1-10 (sredina ± SEM) | | | | |
| Anal pain at defection, n (%) | 13 (68.42) | 12 (63.16) | 28 (93.33) | 27 (90) |
| Boj analne regije tokom defekacije, n (%) | 6 (31.58) | 7 (36.84) | 2 (6.66) | 3 (10) |
| Odsustvo bola analne regije tokom defekeacije, n (%) | 11 (57.89) | 12 (63.16) | 28 (93.33) | 25 (83.33) |
| Visible anal bleeding/Vidljivo analno krivarenje, n (%) | 8 (42.11) | 7 (36.84) | 2 (6.66) | 5 (16.67) |
| No visible anal bleeding, n (%) | | | | |
| Intensity of anal bleeding 1-10 (mean ± SD) | 3.05 ± 0.46 | 1.63 ± 0.19** | 2.93 ± 0.15 | 2.13 ± 0.17 |
| Intenzitet analnog krivarenja 1-10 (sredina ± SD) | | | | |
| Grade of hemorrhoids (mean ± SEM) | 2.16 ± 0.68 | 1.68 ± 0.58* | 2.7 ± 0.54 | 2.73 ± 0.52 |
| Stepen hemoroida (sredina ± SEM) | | | | |

*Statistically significant difference at the level p < 0.05 at 14th day of treatment compared to baseline; #statistically significant difference at the level p < 0.05 at the same time compared to Avaricon® group

Regarding the assessment of safety and tolerability of applied treatment, only one patient in the Avaricon® group reported a side effect, while none of them experienced side effects in the placebo group, both measured at the end of a 14-day protocol and 7 days later. Furthermore, in regard to the tolerability, 50% of the subjects have answered “very good” and 50% “good” in the Avaricon® group, while in the placebo group one patient defined tolerability of treatment as “very good”, 16 as “good”, 7 patients as “poor” and 1 patient as “very poor”. When assessing improvement of symptoms after the treatment, most of the patients (n = 14 after the treatment, n = 13 seven days after treatment cessation) in the Avaricon® group answered “better”, while the rest answered "no change". Also, most of the patients (n = 14) treated with the placebo answered “no change”, while 7 of them reported “better” and even 4 described it as “worse”.

Compliance and degree of adherence of the study population during Avaricon® Hemor treatment compared with the placebo

Overall assessment of compliance, by analyzing the usage of Avaricon® Hemor/placebo, 7 and 14 days after the beginning of treatment, indicated favorable compliance in both groups. A total of 94.74% of patients applied Avaricon® Hemor cream analy 3 times a day and used the whole tube of the examined cream. Also, 96.67% patients used the placebo analy 3 times a day, while 93.34% of them used the whole tube. Patients using Avaricon® Hemor cream showed more adherent with significantly lower number of patients who stopped treatment when feeling either better or worse (p < 0.05).

Discussion

The main goal of all medical strategies for the treatment of hemorrhoidal disease is reduction of perianal pain, itching, tenesmus, and bleeding, rather than improvement in anal canal [1, 15]. Literature data suggest that agents possessing analgesic, local anesthetic, anti-inflammatory and venotonic properties may play a role in the management of this common gastrointestinal disease [8, 16]. Despite the numerous available topical formulations, there is insufficient and poor quality evidence regarding their efficacy, indicating the necessity for further investigation.
evaluation via randomized controlled trials [8]. Throughout the history, topical application of plant-derived products such as extracts, oils etc. has been recognized to heal hemorrhoids, while in recent years attention has been directed to HA [1, 16]. Therefore, we aimed to reveal if Avaricon® Hemor that contains SH, calendula flower extracts (CE), dry hamamelis extract (HE) and essential oil from mentha piperita (MPO) may be efficient in reducing symptoms and improving hemorrhoidal disease.

Our results showed that a 14-day application of both Avaricon® Hemor and the placebo per se, were efficient in reducing anal pain, thus suggesting that use of any type of cream may alleviate symptoms of hemorrhoids to a certain extent [1, 12]. Baseline higher pain intensity in the Avaricon® group was markedly decreased after the treatment, leading to more prominent pain alleviation in comparison to the placebo. Positive effects of Avaricon® Hemor were also evidenced by a decrease in bleeding intensity and grade of hemorrhoids in the Avaricon® group. Moreover, as estimated by VAS, Avaricon® Hemor provided a greater relief of anal pain and pain during defecation, as well as a decline in intensity of bleeding in comparison to the placebo cream. In summary, Avaricon® Hemor cream showed to be significantly superior to the placebo in most of the symptoms, thus improving discomfort and patients’ quality of life.

Table 3. Visual analogue scale for the assessment of Avaricon® Hemor efficacy

| Parameter/Parameter | Avaricon® group/Placebo grupa | Placebo group/Placebo grupa |
|---------------------|-------------------------------|----------------------------|
|                     | Baseline Početne vrednosti | After 14 day Nakon 14 dana |
| Anal pain intensity (mean ± SEM) | 27.47 ± 6.27 | 8.63 ± 2.25** | 18.33 ± 2.54 | 11.53 ± 1.79 |
| Intensity of pain at defection (mean ± SEM) | 28.89 ± 6.45 | 7.58 ± 2.03** | 16.63 ± 2.41 | 10.27 ± 1.44 |
| Intensity of bleeding (mean ± SEM) | 16.95 ± 3.91 | 4.26 ± 0.74 | 11.6 ± 1.9 | 6.43 ± 1.14 |

*aStatistically significant difference at the level p < 0.05 at 14th day of treatment compared to the baseline

The astringent potential of plant-derived constituents of Avaricon® Hemor thus heals mucous membranes due to the presence of tannins, which probably promotes vein elasticity and exerts vasoconstrictor activity in the perianal area [21]. Another advantage of CE, HE and MPO in our formulation is based on their capacity to prevent the breakdown of HA through both antioxidant activity and hyaluronidase inhibition [12, 26]. Furthermore, plant extracts and essential oils increase the potency of SH, since they are able to act against a number of pathogenic bacteria that produce hyaluronidase [12, 27–29].

Assuming that providing safety of the treatment strategy represents a major world health concern, we wanted to find out if our medical preparation is associated with the occurrence of adverse effects. In the current research, neither significant adverse effects related to treatment nor other safety related issues were observed. A difference in favor of Avaricon® Hemor was found when patients assessed the tolerability of treatment. In fact, all patients treated with Avaricon® Hemor scored the tolerability as “good” or “very good”, while none of them scored it as “poor” or “very poor” as it was noticed in the placebo group. A notably better tolerability profile in the Avaricon® group, apart from a more prominent improvement of symptoms evaluated by patients, undoubtedly indicates the advantage of Avaricon® Hemor cream. It is well documented that extensive use of HA in numerous drug formulations is due to its biodegradability, biocompatibility, non-toxicity and non-immunogenicity [30]. Our results are in correlation with a previously conducted investigation which also proved the efficacy and safety of topical gel with SH in combination with tea tree oil and methylsulfonylmethane [12].

The second part of our research assessed the compliance and adherence of patients using the examined medication. It has been considered that treatment non-adherence might be a problem for patients with chronic diseases who have to use a time-consuming topical drug [31]. Data suggest that adherence rates to topical treatments are low, although gels and creams are considered more acceptable among topical formulations [32]. Moreover, we noticed that the majority of patients (94.74%) who applied Avaricon® Hemor cream were...
fully adherent to the prescribed therapy and they did not stop using it when they felt better or worse. Treatment effectiveness of Avaricon® Hemor supports the data obtained for satisfactory adherence, indicating that patients are more likely to continue using the therapy if they believe it to be beneficial.

**Conclusion**

Our results showed that treatment with Avaricon® Hemor was more effective and safe in comparison to the placebo, with a greater potential to reduce numerous symptoms of hemorrhoids. This study provides a rational basis for implementation of Avaricon® Hemor in the management of hemorrhoidal disease, either alone or as an additional therapy following invasive procedures. Nevertheless, a long-term follow-up study is certainly necessary with more participants to completely establish all the therapeutic possibilities of Avaricon® Hemor in this common anorectal condition.

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