THE PERFORMANCE OF BIOAPIFIT® ANTI HEMORRHOIDAL OINTMENT COMPARED TO ACIDOSALUS® SUPPOSITORIES IN THE TREATMENT OF HEMORRHOIDAL DISEASE

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Objective / Purpose: Hemorrhoids are a very common anorectal condition defined as the symptomatic enlargement and distal displacement of the normal anal cushions. The objective of this study was assessment of the efficacy of Bioapifit® anti hemorrhoidal ointment for the treatment of hemorrhoids of grade 1 to 3 compared to Acodosalus® suppositories applied under the same condition.

Materials and methods: The experimental group consisted of 40 participants was treated with Bioapifit® ointment applied externally three times a day onto clean perianal area and rectally once a day for 10 consecutive days. The control group also consisted of 40 participants was treated with Acodosalus® suppositories are applied rectally once a day (before bedtime) for 10 consecutive days.

Results: Ten days external and rectal application of Bioapifit® ointment resulted in significant decrease of all the symptoms of haemorrhoidal disease at third day of the treatment while in the end of the treatment overall subjective discomfort decreased for more than 96%. Clinical cure was observed in 85% of the patients. Acidosalus suppositories applied rectally for ten days also promoted significant decrease of all the symptoms while in the end of the treatment overall subjective discomfort decreased for app 77%. Clinical cure was confirmed in 67.5% of the patients.

Conclusion / Discussion: Physical parameters like low pH, high osmolarity/low water activity, high viscosity, greasiness, coating and lubricating effect resulted in significant decrease of the symptoms of hamorrhoidal disease such as bleeding, itching, irritation, and pain as well as wound infection.

Keywords: hemorrhoidal disease, honeybee's products, herbal macerate

INTRODUCTION

Haemorrhoids are a very common anorectal condition defined as the symptomatic enlargement and distal displacement of the normal anal cushions (Kaidar-Person et al. 2007; Lohsiriwat, 2012). The prevalence of hemorrhoidal disease ranges from 4.4% to 12.8% in normal adult populations and about 40% in patients with symptoms of anal diseases (Johanson and Sonnenberg, 1990). In both sexes, peak prevalence occurred between age 45-65 years and the development of hemorrhoids before the age of 20 years was unusual (Kaidar-Person et al. 2007; Lohsiriwat, 2012). Age, the venous circulation disorders, chronic constipation, sedentary lifestyle, a diet low in fibbers, spicy foods and alcohol intake are common risk factors for the development of haemorrhoids (Riss et al., 2012).

Hemorrhoids are graded based on their appearance and degree of prolapse, known as Goligher's classification: (1) First-degree haemorrhoids (gradeI): The anal cushions bleed but do not prolapse; (2) Second-degree haemorrhoids (grade II): The anal cushions prolapse through the anus on straining but reduce spontaneously; (3) Third-degree

haemorrhoids (grade III): The anal cushions prolapsed through the anus on straining or exertion and require manual replacement into the anal canal; and (4) Fourth-degree haemorrhoids (grade IV): The prolapse stays out at all times and is irreducible.

Therapeutic treatment of haemorrhoids ranges from dietary and lifestyle modification to radical surgery, depending on degree and severity of symptoms (Lohsiriwat, 2012; Kaidar-Person et al., 2007, Sanchez and Chinn, 2012).

Recently the preparations based on honey, glycerin, beeswax and herbal oil/oil macerates have been used to alleviate the symptoms of haemorrhoidal disease with comparable or better results compared to the standard local therapy and are shown to significantly reduce pain and defecation discomfort as well as bleeding and itching severity (Al-Waili et al., 2006; Odukoya et al. 2007; Oreščanin et al., 2018) without causing any side effects. Based on that fact the aim of this study was evaluation of the potential of Bioapifit® anti-haemorrhoidal ointment and Acisosalus® suppositories for symptomatic treatment of haemorrhoidal disease in adult population.

MATERIALS AND METHODS

Study Design

The study was conducted as Prospective, randomized, controlled, comparative study. The study was conducted at the following locations: FINDRI GUŠTEK HEALTHCARE INSTITUTION, Ninska 5a, Sesvete, Croatia and FAMILY MEDICINE CLINIC, Vilima Korajca 19 Zagreb, Croatia. The study protocol was approved by the Ethics Committee of Findri Gustek Health Care Center with EudraCT number 2019-001055-38.

The investigator recruited the patients based on their medical history, following the predefined inclusion and exclusion criteria. The exclusion criteria were pregnancy, breast-feeding, presence of malignant and inflammatory bowel diseases, history of allergy to any ingredient of the product, hemorrhoids of grade 4, less than 18 years of age and previous history of anorectal surgery. In total, 80 patients were included of 100 patients screened. After the informed consent has been signed at Visit 1, Day 1 the patients included are assigned a permanent identification number (by a nurse) and assigned to either experimental or control group based on the randomization code. All the patients are subjected to the following procedures: review of the general feeling in a questionnaire, review of medical history and allergy data, review of medication history, performing complete physical examination, determination of the grade of haemorrhoidal disease, informing patients of study restrictions and compliance requirements, withdrawing from being involved in the medical device testing, data on concomitant participation in a clinical study involving any other medical product or device.

Patients of the experimental group were given one tube (50 mL) of Bioapifit® anti-haemorrhoidal ointment with applicator and instructions for use. Patients of the control group were given a box of Acidosalus® anti-haemorrhoidal suppositories (10 suppositories, 3 g each) together with instruction for use.

Diagnosis and degree of haemorrhoidal disease was made based on medical examination by Principal investigators and rating of the symptoms by the patients. The investigator evaluated the clinical efficacy of the medical device used as cure, improvement

or failure. The participants were asked whether they have experienced any side effects throughout the study.

Treatment

The experimental group was treated ten days with Bioapifit® anti haemorrhoidal ointment which was applied in thin layer onto clean perianal area three times a day and rectally once a day (before bedtime) using the applicator.

The control group also consisted of 40 patients was treated with Acidosalus® anti haemorrhoidal suppositories also for ten days. One suppository (3 g) was applied once a day (before bedtime) into the rectum.

Follow-up period for both groups was from Day 11 to Day 30. The degree of the disease in both groups was assessed at baseline, and after 3, 5 and 10 days of the treatment. The evaluation of the patients before and following the therapy was done in terms of pain (0-10), defecation discomfort (0-10), bleeding severity (0-4), anal itching severity (0-4) and overall subjective discomfort (0-10).

Description of investigational products

Bioapifit® anti hemorrhoidal ointment is homogeneous, greasy, viscous mass of characteristic herbal odor and olive green color with pH of 4.87, density of 0.9645 g/cm^3 and viscosity of 21136 cP. It consists of the following ingredients: honey; beeswax (*Cera flava*); glycerol; oil extracts of the plant species: the areal part of yarrow (*Achillea millefolium* L.), sage leaves (*Salvia officinalis* L.), plantain leaves (*Plantago major* L.), oak bark (*Quercus robur* L.), olive leaves (*Olea europaea* L.), marigold flowers (*Calendula officinalis* L.), chamomile flowers (*Matricaria chamomilla* L.), the areal part of knotweed (*Polygonum aviculare* L.); Essential oils: Australian tea tree (*Melaleuca alternifolia*), thyme (*Thymus vulgaris* ct. thymol), oregano (*Origanum vulgare*). Detail description of ointment preparation was presented in the previous paper (Oreščanin et al., 2018.)

Acidosalus® suppositories are composed of: Hydrogenated coco glycerides, propylene glycol, glyceryl monostearate, cetostearyl alcohol, polysorbate 60, lanolin alcohol, panthenol, menthol, tocopheryl acetate, *Ruscus aculeatus*, *Urtica dioica*, benzoic acid, *Lactobacillus acidophilus* (min. $1x10^6$ cfu/suppository). Each box contains 10 suppositories of 3 g each packed separately in PE-HD blisters.

Statistical analysis

Statistical analysis was performed using STATISTICA 12.0 software package. The required sample size was calculated by Power analysis method. Frequencies and percentages were calculated for each categorical variable using frequency tables. Potential differences between the groups of categorical variable were determined using χ2 Test. Basic statistical parameters were determined for each continuous variable. The Shapiro-Wilk W-Test was used to determine the normality of distribution of continuous variables, while Levene's Test was used for homogeneity of variances. The t test was used to determine the difference between mean values of two groups (initial and final values) with normally distributed continuous variables, while the analysis of variance and Newman-Keuls test

were used for the assessment of difference among three and more groups. Before carrying out the above-mentioned statistical analyses of data, logarithmic transformation was used to deal with the variables which deviate from the normal distribution. To determine the dependence of the dependent variable on the chosen predictor variables, multiple regression analysis and general regression models were applied. The p-value of less than 0.05 (p<0.05) will be considered statistically significant in all measurements.

RESULTS

Bioapifit® anti haemorrhoidal

Description of the population

The age range of the patients treated with Bioapifit® anti hemorrhoidal ointment from 25 to 81 years (49.5±11.8) with median of 49 years. Body mass index ranged from 18.5 to 39.9 kg/m² (25.5±4.3).
72.5% of the Bioapifit® treated population were females and 27.5% males. According to the education level the majority of them had College/University Degree or Master of Arts (45%) followed by secondary education (32.5%). 47.5% of them suffered from constipation and among 77.7% of them sedentary type occupation or lifestyle prevailed. 70% of them were not engaged in any sporting activity. Majority of them consumed boiled food preferentially (80%). The supplements with laxative effect consumed 60% of the population (50% occasionally and 10% regularly).
For the assessment of the influence of the predictor variables onto the overall subjective symptoms of the hemorrhoidal disease the general regression model expressed as Pareto charts of t-values (Fig. 1) and multiple regression analysis were applied.
According to the Pareto chart of t-values the variables with the highest, statistically significant influence on the overall subjective symptoms of the hemorrhoidal disease were body mass index, sedentary lifestyle, constipation and education level. Indeed, the patients with BMI higher than 26 kg/m² had significantly higher (p=0.0001) mean value of overall subjective discomfort rate (5.8±2.3) compared to those with BMI lower than 26 kg/m² (4.1±1.3). Those with prevailing sedentary occupation or lifestyle had also significantly higher value (p= 0.04726) of overall subjective discomfort rate (5.7±1.8) compared to active lifestyle (4.7±1.3). The patients that suffer from constipation showed mean value of overall subjective discomfort rate of 6.1±1.8 compared to those with no problems with constipation (4.3±1.8) (p<0.0001). The patients with the highest education level had the highest value of overall subjective discomfort rate (6.0±1.8) which was probably connected with mostly sedentary types of occupation.
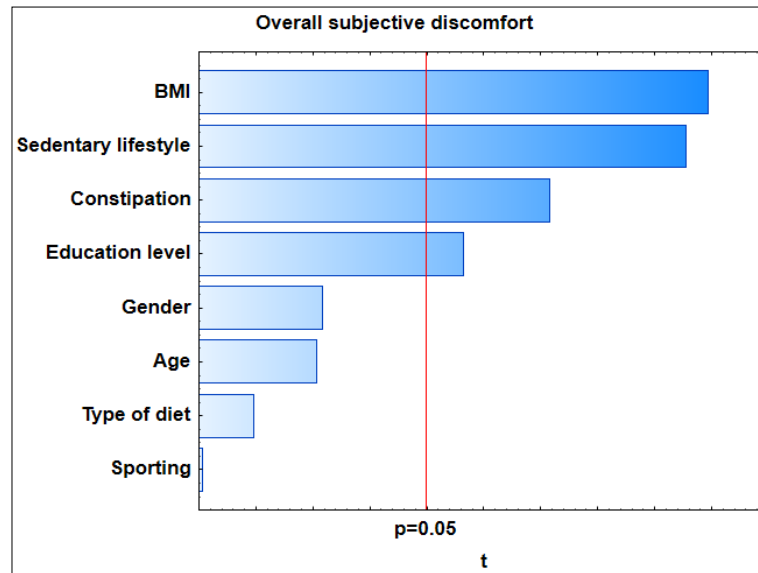
Figure 1. Pareto chart of t-values testing for the influence of the predictor variables on the rate of overall subjective discomfort of the hemorrhoidal disease in the experimental group patients.

The results of multiple regression analysis conducted on the experimental group showed very good, statistically significant correlation between the selected predictor variables and overall subjective discomfort of hemorrhoidal disease (R= 0.81; p p<0.0000). Based on the values of the beta coefficients and their significance among the predictor variables BMI (β=0.41, p<0.0000), sedentary lifestyle (β=0.37, p=0.0001), constipation (β=0.28, p=0.0030) and education level (β=0.22, p=0.0232) showed statistically significant contribution.

Similar results were obtained in the previous study (Oreščanin et al., 2018) considering the influence of BMI and chronic constipation. It was confirmed that the patients with the highest value of overall subjective discomfort (rated 8 and 9) had the highest values of BMI (29.3±3.5) while those with mean value of the overall subjective discomfort of 5 had BMI 23.5±0.2. The patients that rated their overall subjective discomfort with 8 and 9 all suffered from constipation. Moreover, another study (Riss et al., 2012) revealed that sedentary lifestyle and chronic constipation represent significant risk factors for the development of hemorrhoidal disease.

Treatment efficiency

Before the treatment 62.5% of the participants had first grade hemorrhoidal disease 22.5% of them second grade and 15% of the participants third grade hemorrhoidal disease. Following the ten days of the treatment with Bioapifit® anti hemorrhoidal ointment complete disappearance of all the symptoms was confirmed in 85% of the patients while in 15% of them only mild symptoms persisted classified as first degree hemorrhoids.

At baseline, the mean values and standard deviations for the symptoms like pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective

discomfort were 5.0±1.8, 5.2±1.9, 1.6±1.0, 2.3±1.1 and 5.2±1.9, respectively (Figure 2). Following only three days of the treatment all the parameters decreased significantly to 1.9±1.2 for pain, 2.2±1.3 for defecation discomfort, 0.5±0.6 for bleeding, 1.0±0.8 for anal itching and 2.1±1.1 for overall subjective symptoms. Further decrease of all the parameters was obtained following the fifth day of the treatment. Median value for pain, defecation discomfort and overall subjective symptoms was 1 and for bleeding and itching 0. At 10th day the median value of all the symptoms including overall subjective discomfort was 0. The mean values and standard deviations were 0.2±0.7, 0.3±0.7, 0.0±0.2, 0.1±0.3 and 0.2±0.7 for pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective discomfort, respectively.

Analysis of variance showed significant difference for all the symptoms among the treatment periods. The results of Newman-Keuls test showed statistically significant difference between baseline and all treatment periods for all five parameters. Moreover, significant difference was also observed between each pairs of the treatment periods for all the parameters with exception of bleeding severity between the fifth and tenth day.
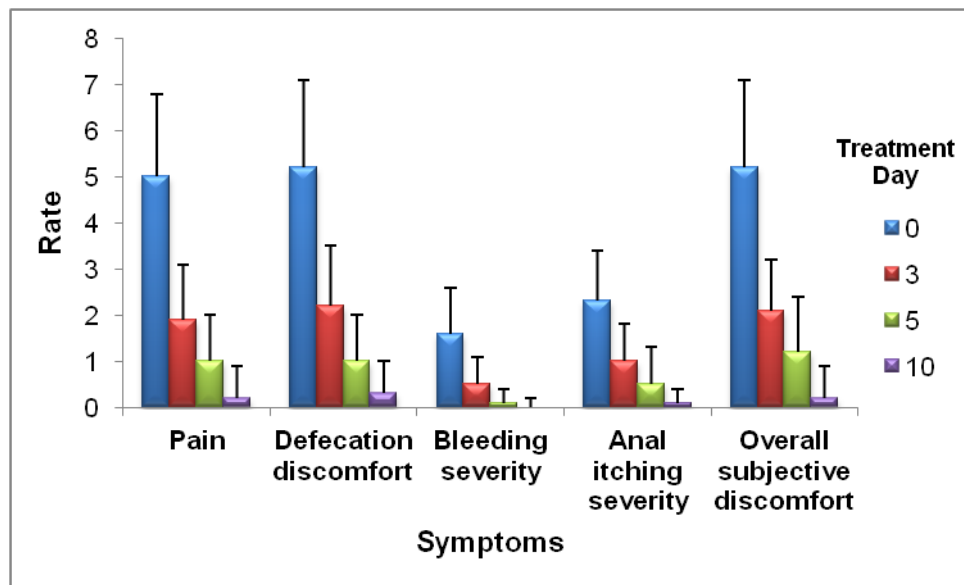

Figure 2. Mean values and standard deviations of the scores for each symptom of the hemorrhoidal disease and overall subjective discomfort prior and following 3, 5 and 10 days of the treatment with Bioapifit® anti-hemorrhoidal ointment

Clinical cure (all the symptoms rated 0) was observed in 85% of the participants while in another 15% clinical improvement was observed.

Acidosalus anti haemorrhoidal suppositories

Description® of the population

Age range for Acidosalus® suppositories treated group was from 25 to 81 year (51.9±19.1 years). Body mass index ranged 18 to 40.3 kg/m² (26.0±4.7 kg/m²). Among the tested population 55% of them were females and 45% males. Among 40 participants 50% of them finished secondary education and 37.5% of them have College/University Degree or Master of Arts.

37.5% of them suffer from constipation and 87.5% of them prefer sedentary type of occupation or lifestyle. 80% of them are not engaged in any sport activity while 12.5% of them perform exercise at least once a week. Prevailing diet type was boiled food (75% of the participants). 30% of the participants take the supplements with laxative effect.

The results of general regression model expressed as Pareto chart of t-value identified the sedentary type of lifestyle/occupation, BMI and constipation as the significant contributor to the overall subjective discomfort of the hemorrhoidal disease (Fig. 3).
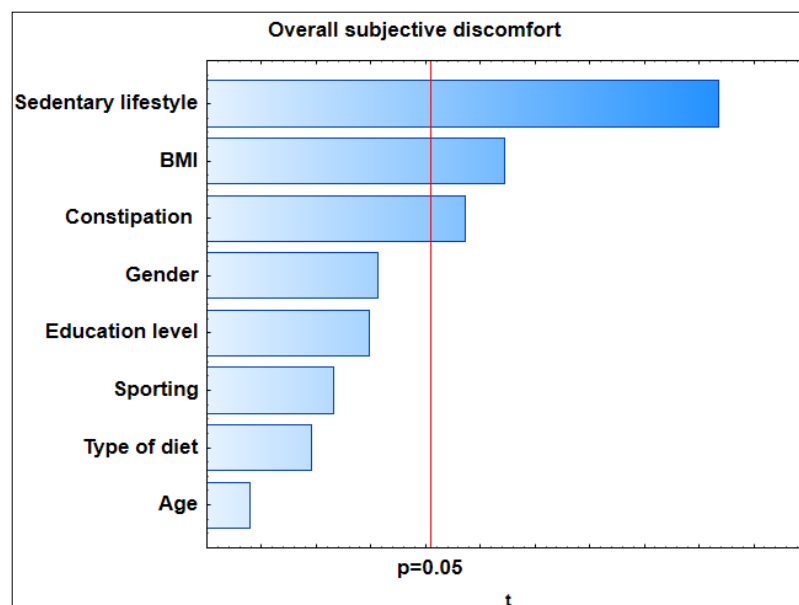

Figure 3. Pareto chart of t-values testing for the influence of the predictor variables on the rate of overall subjective discomfort of the hemorrhoidal disease

Multiple regression analysis revealed statistically significant correlation between the selected predictor variables and the overall subjective symptoms of hemorrhoidal disease (R= 0.79; $p<0.0001$). According to the beta coefficients and their significance sedentary lifestyle or occupation (β=0.59; p=0.0001), BMI (β=0.26; p=0.0427) and constipation (β=0.22; p=0.0472) had the highest, statistically significant influence on the total correlation.

Treatment efficiency

Considering the grade of the hemorrhoidal disease before the treatment 75% of the patients suffered from first grade hemorrhoids, while 12.5% had second grade and another 12.5% third grade hemorrhoids. Following the treatment all the symptoms disappeared in 62.5% of the patients and another 37.5% of them exhibited only slight symptoms rated as grade I.

At baseline, the mean values and standard deviations for the symptoms like pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective discomfort were 4.3±1.8, 4.2±1.8, 1.0±0.7, 3.2±1.3 and 4.4±1.9, respectively (Figure 4). After only three days of the treatment all the parameters decreased significantly to 2.7±1.7 for pain, 2.6±1.6 for defecation discomfort, 0.4±0.7 for bleeding, 1.7±1.1 for anal itching and 2.5±1.5 for overall subjective symptoms. Between the third and the fifth day of the treatment further decrease was also observed for all measured parameters. At 10th the mean values and standard deviations were 1.1±1.3, 1.1±1.3, 0.1±0.2, 0.6±0.7 and 1.0±1.3 for pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective discomfort, respectively.

Analysis of variance showed significant difference for all the symptoms among the treatment periods. The results of Newman-Keuls test showed statistically significant difference between baseline and all treatment periods for all five parameters.
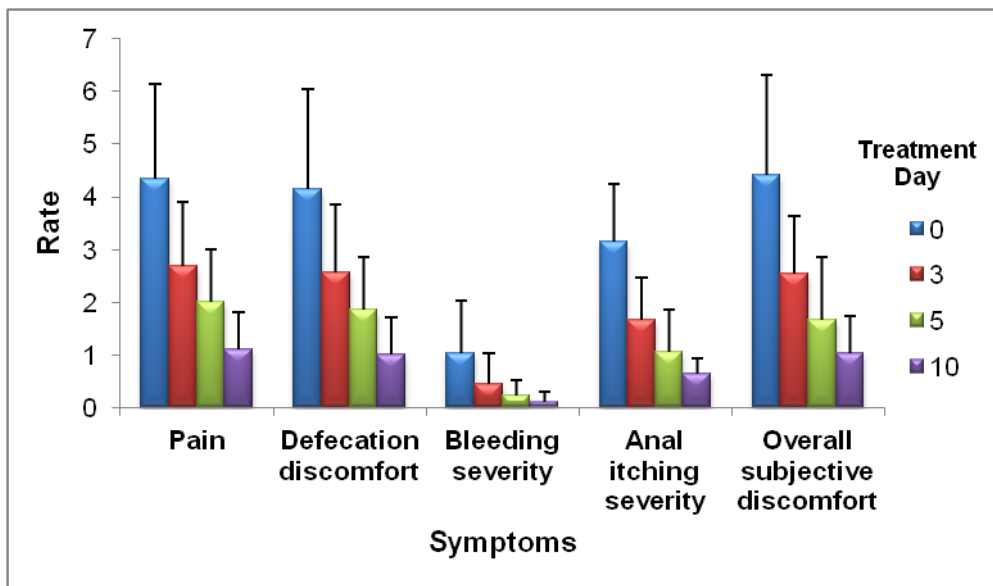

Figure 4. Mean values and standard deviations of the scores for each symptom of the haemorrhoidal disease and overall subjective discomfort prior and following 3, 5 and 10 days of the treatment with Acidosalus® anti hemorrhoidal suppositories

Following the treatment, 62.5% of the participants showed no symptoms of haemorrhoidal disease while in other 37.5% clinical improvement was obtained

Comparison of two treatment approaches

Both treatment groups were of similar age, BMI and lifestyle. However, t-test showed significant difference in the initial values of all the symptoms of hemorrhoidal disease. Since, direct comparison of the mean values of the rate of the selected symptoms of two treatment approaches following each treatment period wouldn't be appropriate approach due to differences in the initial values in two tested groups the percentage of the decrease of the mean value of each symptom following each treatment time was calculated for both groups and the differences between the percentages were tested by χ^2 test (Table 1-3).

Following third day of the treatment the participants treated with Bioapifit® anti hemorrhoidal ointment reported decrease in the mean values of the symptoms from 56.5% to 68.8%. In the case of Acidosalus® suppositories this decrease ranged from 37.9% to 57.5%. Although, Bioapifit® ointment performed slightly better there was no statistically significant difference between these two groups for any of the symptoms (Table 1).

After fifth day of the treatment (Table 2) Bioapifit® ointment perform better considering pain (p=0.0243) and defecation discomfort (p=0.0293). However, there was no significant difference in the percentage of decrease of the overall subjective discomfort (p=0.2358).

In the end of the (Table 3) treatment Bioapifit® ointment perform significantly better in term of pain (p=0.0171) and defecation discomfort (p=0.0475). However, there was no significant difference in the percentage of decrease of the overall subjective discomfort (p=0.0563).

Table 1. Percentage of the decrease of the mean value for each symptom of hemorrhoidal disease following third day of the treatment with Bioapifit® ointment (BO) or Acidosalus® suppositories (AS) and the results of χ^2 test between those two groups

Symptom	BO	AS	χ^2	p
Pain	62.0	37.9	3.7	0.0543
Defecation discomfort	57.7	38.3	2.3	0.1303
Bleeding severity	68.8	57.5	0.6	0.4146
Anal itching severity	56.5	47.2	0.3	0.5428
Overall subjective discomfort	59.6	42.4	1.7	0.1885

Both approaches have received good ratings by the patients. The treatment with Bioapifit® ointment showed slightly better rating (4.9±0.3) compared to Acidosalus® suppositories (4.7±0.5). However, this difference was not statistically significant (t= 1.4; p=0.0856). Median rating for both products was 5.

When comparing the clinical efficiency it seems that Bioapifit® ointment performed better compared to Acidosalus® suppositories (Table 4). However, based on the results of χ^2 test there was no statistically significant difference between these two groups.

Table 2. Percentage of the decrease of the mean value for each symptom of hemorrhoidal disease following fifth day of the treatment with Bioapifit® ointment (BO) or Acidosalus® suppositories (AS) and the results of χ^2 test between those two groups. *statistically significant

Symptom	BO	AS	χ^2	p
Pain	80	53.8	5.1	0.0243*
Defecation discomfort	80.8	55.6	4.8	0.0293*
Bleeding severity	93.8	77.5	3.1	0.0783
Anal itching severity	78.3	66.7	0.8	0.3621
Overall subjective discomfort	76.9	62.2	1.4	0.2358

Table 3. Percentage of the decrease of the mean value for each symptom of hemorrhoidal disease following tenth day of the treatment with Bioapifit® ointment (BO) or Acidosalus® suppositories (AS) and the results of χ^2 test between those two groups. *statistically significant

Symptom	BO	AS	χ^2	p
Pain	96	74.6	5.7	0.0171*
Defecation discomfort	94.2	75.9	3.9	0.0475*
Bleeding severity	100	90	2.4	0.1238
Anal itching severity	95.7	79.7	3.4	0.0661
Overall subjective discomfort	96.2	76.7	3.7	0.0563

Table 4. The percentages of the patients based on clinical efficiency following ten days of the treatment with Bioapifit® anti hemorrhoidal ointment (BO) and Acidosalus® anti hemorrhoidal suppositories (AS) and the results of χ^2 test between these two groups

Clinical efficacy	BO	AS	χ^2	p
Clinical cure	85	62.5	2.8	0.0932
Clinical improvement	15	37.5	0.2	0.6280

None of the patients from either Bioapifit® or Acidosalus® group experienced any discomfort or adverse effect including allergic reaction, worsening of the existing or the occurrence of new symptoms during the treatment. This was also confirmed by Principal investigators by physical examination. The ointment treated group reported decrease in pain and itching 10 to 20 minutes after the application of the ointment. Both groups with the overall subjective symptoms rated from 2-4 reported significant improvement after only two days of the application.

DISCUSSION AND CONCLUSIONS

Bioapifit® anti hemorhoidal ointment

Conducted study confirmed high efficiency of Bioapifit® anti hemorrhoidal ointment in the treatment of the hemorrhoids of grade I to III with the reduction of overall subjective discomfort for more than 96% after 10 days of external and rectal application. Physical parameters like low pH (due to the presence of honey and macerate), high osmolarity/low water activity (due to the presence of honey), high viscosity, greasiness and coating effect (due to the presence of oil macerate, glycerin and beeswax) as well as lubricating effect (due to the presence of honey, oil macerates and glycerine) of Bioapifit® anti hemorrhoidal ointment resulted in the alleviation of the symptoms of hemorrhoidal disease such as bleeding, itching, irritation and pain as well as wound infection due to: the creation of the protective coating on the damaged perianal and rectal mucosa enabling its recovery and preventing further irritation; the creation of unfavorable conditions for the growth, adhesion and multiplications of the pathogens (low pH, high osmolarity, low water activity, coating effect); alleviation of pain and discomfort during defecation due to lubricating effect.

It was reported that pH of the wound has critical influence on its closure potential since the wounds with pH higher than 8 showed no reduction in size (Gethin et al., 2008). Honey with its acidic pH ranging between 3.2 and 4.5 supported recuperation of the damaged mucosa by optimizing wound pH (Alam et al., 2014). Besides, osmotic effect of sugars/low water activity created the environment unfavorable for pathogens growth and development of the infection that also speeded up recovery process. Beeswax provided excellent protective coating which prevented the contact between stool and the damaged mucosa and prevented further irritation and infection of the damaged area. The presence of glycerol and honey together with oil macerates increased lubrication which resulted in the reduction of pain and discomfort during defecation.

Besides, previous studies showed beneficial effect of the astringent plants rich in soluble tannins in the treatment of wounds including bleeding hemorrhoids (Odukoya et al., 2007; Abascal and Yarnell, 2005) by physical activity of shrinking of the hemorrhoids and by forming the protective coating over damaged tissue that resulted in the reduction of bleeding. For that purpose oil macerates of the plants with strong astringent properties: yarrow (*Achillea millefolium* L.), plantain leaves (*Plantago major* L.), sage leaves (*Salvia officinalis* L.), oak bark (*Quercus robur* L.), olive leaves (*Olea europaea* L.), the areal part of knotweed (*Polygonum aviculare* L.) were employed in the tested medical device. Furthermore, the macerates of marigold flowers (*Calendula officinalis* L.) and chamomile flowers (*Matricaria chamomilla* L.) were used due to its soothing and calming effect (Oreščanin et al, 2018).

Previous studies using the products based on honey, herbal oil and beeswax were found safe and clinically effective in the treatment of hemorrhoidal disease (Al-Waili et al. 2006; Oreščanin et al, 2018).

Al-Waili et al. (2006.) conducted prospective pilot study with the ointment consisted of 50% of honey, 29% of olive oil, and 21% of beeswax on the patients with hemorrhoids. The ointment significantly reduced bleeding and relieved itching and pain. The initial

values of the scores for pain, bleeding and itching were reduced from 2.77 ± 2.07, 1.6 ± 0.69 and 1.57 ± 0.78, respectively to 0, 0.2 ± 0.42 and 0 after four weeks of the treatment. No side effect was reported with use of the mixture. It was concluded that mixture of honey, olive oil, and beeswax is safe and clinically effective in the treatment of hemorrhoids.

Previous study using Bioapifit® anti hemorrhoidal ointment (Orescanin et al, 2018) on 66 patients with hemorrhoids of grade I to III resulted in complete dissapearence of all the symptoms following ten days of external (3 times daily) and rectal (once a day) application. A significant reduction of all the symptoms was obtained third day of the treatment with reduction of pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective symptoms for 66.7%, 63.8%, 72.7%, 50% and 57,1%, respectivelly which was wery similar to the results obtained in the present study (Table 1). No side-effects were observed in any of the patient.

Based on the results of the current study and the previously published data it could be concluded that Bioapifit® anti hemorrhoidal ointment is safe and clinically efficient in alleviating the symptoms of hemorrhoidal disease by physical manner due to coating, pH adjusting, osmotic and lubricating effect.

Acidosalus® suppositories

Conducted study revealed high efficiency of Acidosalus® anti haemorrhoidal suppositories in the treatments of the hemorrhoids of grade I to III with the reduction of overall subjective discomfort for app. 77% after 10 days of the rectal application. The symptoms like pain, defecation discomfort, bleeding severity and anal itching severity decreased for 74.6%, 75.9%, 90% and 79.7% in the end of the treatment. None of the patients reported any side-effect during the course of study. Based on the results it could be concluding that Acidosalus® suppositories are safe and clinically effective in alleviation of the symptoms of hemorrhoidal disease.

Acidosalus suppositories exhibit their effects by physical manner by creating a protective coating which enables recovery of the damaged area and prevent further irritation of the hemorrhoidal region during defecation and friction caused by clothing and sitting due to the presence of Hydrogenated coco glycerides. Moreover, probiotic bacteria *Lactobacillus acidophilus* (La-5) establish healthy balance of the intestinal flora and thus positively affect the intestinal health and consequently prevent and alleviate the symptoms associated with haemorrhoids. Probiotic bacteria also help to maintain acidic pH of the wound essential for its healing process.

Clinical safety

Based on the informations obtained from the patients or by direct examination by Principal investigators it is possible to conclude that tested medical devices (Bioapifit® anti haemorrhoidal ointment, Acidosalus® anti haemorrhoidal suppositories) do not cause any adverse effect and are safe for perianal and rectal administration in the case of Bioapifit® ointment externally three times per day and rectally once a day for the period of ten days and in the case of Acodosalus® suppositories, rectally once a day for the period of ten days.

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