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BIOAPIFIT® ANTI-HEMORRHOIDAL OINTMENT EFFICIENCY - A COMPARISON WITH STANDARD APPROACH

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ABSTRACT

Hemorrhoids are defined as varicosities of the veins of the hemorrhoidal plexus, often complicated by inflammation, pain, thrombosis, and bleeding. The objective of this study was to assess the efficacy of new Bioapifit multi-component ointment consisted of honey, Cera flava, glycerin, the oil macerates of Achilea millefolium L., Plantago major L., Quercus robur L., Salvia officinalis L., Olea europaea L., Polygonum aviculare L., Calendula officinalis L., Matricaria chamomilla L. and essential oils of Melaleuca alternifolia, Thymus vulgaris ct. Thymol and Origanum vulgare for the treatment of hemorrhoids of grade 1 to 3 as well as the comparison to the standard treatment approach. The experimental group consisted of 66 participants was treated with Bioapifit ointment while the control group consisted of 40 participants was treated with Faktu ointment (50 mg/g of policresulene and 10 mg/g of cinchocaine). Either Bioapifit or Faktu ointment was applied externally three times a day for ten days onto clean perianal area and rectally once a day (before bedtime) using appropriate applicator. The evaluation of the patients before and following the therapy was done in terms of pain, defecation discomfort, bleeding severity, anal itching severity and overall subjective discomfort. After three days of the therapy the mean values and standard deviations in the experimental group for pain, defecation discomfort, bleeding, itching and overall subjective discomfort decreased from 6.6±0.9, 6.9±1.0, 2.2±0.7, 2.6±0.6 and 7.0±0.8, respectively to 2.2±0.8, 2.5±1.0, 0.6±0.5, 1.3±0.7 and 3.0±0.8, respectively. At 10th day of the treatment all five parameters were graded 0 by all 66 patients. The control group also showed a significant decrease of all five parameters after only three days of the therapy while in the end of the treatment overall subjective symptoms decreased from 3.8±1.0 to 0.9±0.9. Bioapifit ointment was found superior to Faktu ointment in the treatment of the symptoms of hemorrhoidal disease.

KEYWORDS : Bioapifit ointment, Faktu ointment, hemorrhoids, honeybees products, oil macerates, essential oils

INTRODUCTION

Hemorrhoid is defined as varicosities of the veins of the hemorrhoidal plexus, often complicated by inflammation, thrombosis, and bleeding (Sanchez et al., 2007). It correlate positively with age and more than half of the population of both genders aged 50 years and older will develop hemorrhoidal disease during their lifetime (Johanson et al., 1990). Besides, the venous circulation disorders, chronic constipation, sedentary lifestyle, a diet low in fibers are important risk factors for the occurrence of hemorrhoids (Riss et al., 2012). The prevalence of hemorrhoidal disease is estimated to be between 4.4% and 12.8% in normal adult populations and about 40% in patients with symptoms of anal diseases. The most common symptoms are rectal bleeding, pain associated with thrombosed hemorrhoids, and perianal pruritus. In this work we tested the efficacy of new multi-component ointment for the treatment of hemorrhoids of grade 1 to 3 and compared its efficacy with Factu ointment considered as standard approach. The symptoms of the hemorrhoidal disease depend on the stage. The first stage is accompanied by itching and bleeding during defecation. At this stage, hemorrhoids are not painful. The blood is fresh and appeared only on the surface of the stool. The second stage is accompanied by itching, scarring, bleeding and pain during defecation while hemorrhoids prolapsed outside the canal and return spontaneously. In the third stage of the disease there is no spontaneous return of hemorrhoids into anal canal while the symptoms like pain, itching and bleeding are significantly more pronounced in relation to the second stage. Fourth-degree hemorrhoids are irreducible even with manipulation, accompanied by severe pain and thrombosis. The treatment methods are dependent on the stage of the disease and the severity of the symptoms ranging from non-surgical to surgical approach (Banov et al., 2011; Kaidar-Person et al., 2007). The symptomatic treatment includes the application of softeners, warm sitz bath, the ointment with anesthetic like lidocaine or compresses with hamamelis. The pain resulting from thrombosed hemorrhoids could be treated with non-steroidal anti-inflammatory drugs. Besides, simple incision and clog removal quickly alleviate pain. Injection sclerotherapy with 5%

phenol in vegetable oil will stop bleeding at least temporarily. Larger internal hemorrhoids or those who do not respond to sclerotherapy are treated by rubber band ligation. In the case of mixed internal and external hemorrhoids, only the internal ones are subjected the rubber band ligation. Infrared photocoagulation is useful in the ablation of smaller internal hemorrhoids, hemorrhoids that could not be treated by the rubber band due to pain sensitivity or hemorrhoids that are not cured by banding. Other methods of treatment include the destruction of hemorrhoids by laser, cryotherapy or electrocoagulation. Surgical hemorrhoidectomy is used only for the cases that do not respond to other treatment methods.

Herbal preparations have recently been used to alleviate the symptoms of hemorrhoidal disease with comparable or better results compared to the standard therapeutic approaches and are shown to significantly reduce pain and defecation discomfort as well as bleeding and itching severity (Abascal et al., 2005; Odukoya et al., 2007; Eshghi et al., 2010; Panpimanmas et al., 2010; Panahi et al., 2014; Mosavat et al., 2015).

The aim of this research was evaluation of the potential of Bioapifit anti-hemorrhoidal ointment for the alleviation of the symptoms of hemorrhoidal disease as well as comparison of the efficiency of this product with the standard therapeutic approach applied under the same condition.

MATERIALS AND METHODS

Study Design

The study was designed as the open labeled, randomized, controlled clinical trial. The study protocol was approved by the Ethics Committee of Findri Gustek Health Center. All the participants signed informed consent and completed the questioner.

Patients

Total of 106 patients (42 males and 64 females) ranging from 25 to 89

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years with clinically confirmed hemorrhoidal disease of grade 1 to 3 were included in the study. The exclusion criteria were pregnancy, breast-feeding, presence of malignant and inflammatory bowel diseases, history of allergy to any ingredient of the product, hemorhoids of grade 4, less than 18 years of age and previous history of anorectal surgery. The participants were randomly selected into two groups (experimental and control) with similar age, lifestyle and general health status. The experimental group consisted of 66 and control of 40 patients.

Preparation of the Macerate

All plant material was purchased from the certified supplier (Suban, Strmec Samoborski, Croatia). The quality of herbal material used for the macerate production was in accordance with Ph. Eur criteria requirements. The macerate was prepared from the dried plants and sunflower oil with solid/liquid ratio = 1:5. For the production of the macerate the following plants were used: 20% of areal parts of yarrow (Achillea millefolium L.), 20% of plantain leaves (Plantago major L.), 15% of sage leaves (Salvia officinalis L.), 15% of oak bark (Quercus robur L.), 10% of olive leaves (Olea europaea L.), 10% of the areal part of knotweed (Polygonum aviculare L.), 5% of marigold flowers (Calendula officinalis L.), 5% of chamomile flowers (Matricaria chamomilla L.). Above mentioned proportion of each dried plant was added into stainless steel vessel and mixed thoroughly in order to achieve homogeneity of the sample. After addition of sunflower oil the sample was mixed once again, sealed and extracted by ultrasound for 24 h. Solid/liquid separation was done by filtration.

Preparation of the Ointment

70% of the macerate, 10% of honey, 10% of Cera flava (Kemig, Zagreb, Croatia) and 9% of glycerin were heated until 60°C, mixed slowly for 10 minutes and allowed to cool to 30°C. Pharmaceutical grade essential oils (Pranarom International, Belgium) of Melaleuca alternifolia (0.5%), Thymus vulgaris ct. Thymol (0.3%), and Origanum vulgare L (0.2%) were added into the mixture, mixed thoroughly and packed into Alu-tubes of 50 mL volume.

The final product contains: 10% of honey, 10% of Cera flava, 9% of glycerin, 14% of the oil macerate of Achilea millefolium L., 14% of the oil macerate of Plantago major L., 10.5% of the oil macerate of Quercus robur L., 10.5% of the oil macerate of Salvia officinalis L., 7% of the oil macerate of Olea europaea L., 7% of the oil macerate of Polygonum aviculare L., 3.5% the oil macerate of Calendula officinalis L., 3.5% the oil macerate of Matricaria chamomilla L.; essential oils: 0.5% of Melaleuca alternifolia, 0.3% of Timus vulgaris ct. Thymol, 0.2% of Origanum vulgare.

Treatment Protocol

The patients were randomly selected into two groups. The experimental group was treated 10 days with the Bioapifit antihemorrhoidal ointment. The ointment was applied externally three times a day onto clean perianal area and rectally once a day (before bedtime). The control group was treated with Faktu ointment (Takeda GmbH, Singen, Germany) consisted of 50 mg/g of policresulene and 10 mg/g of cinchocaine which was used in the same way as described for Bioapifit ointment. 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).

Statistical Analysis

For statistical evaluation Statistica 11.0 software package was employed. The description of the treated population was done by basic statistics and frequency tables. Statistical significance was set to p<0.05 in all the tests performed. The differences among three and more groups (treatment time) was assessed by Newman-Keuls test and between two groups by t-test. The influence of the predictor variables on the degree of the disease was tested by

Multiple regression method and General regression model (Oreščanin et al., 2015).

RESULTS AND DISCUSSION Description of the Population

The experimental group consisted of 43 females and 23 males (Table 1). The grade 2 hemorrhoids were diagnosed in 28 and grade 3 in 38 of the participants. The majority of the population suffer from constipation (77.3%) and 75.8% of them had sedentary lifestyle.

The basic statistical parameters for age and body mass index and the results of t-test between males and females participants were presented in Table 2. The experimental population ranged from 27 to 69 years of age (48.2±13.4). Females were significantly younger (45.9±13.1) compared to males (52.7±13.0). The body mass index (BMI) ranged from 22 to 35 (27.6±2.7). There was no significant difference between males and females.

The results of multiple regression analysis conducted on the experimental group (Table 3) showed good, statistically significant correlation between the selected predictor variables and overall subjective discomfort of hemorrhoidal disease (R=0.63; p<0.00096). Among the predictor variables BMI and constipation had only statistically significant contribution.

Table 1. The frequency table for selected predictor variables for experimental and control group.

Variable	Sub-group	Experimental		Control	
		Ν	%	Ν	%
Gender	F	43	65.2	21	52.5
	М	23	34.8	19	47.5
Grade	1	0	0	36	90
	2	28	42.4	4	10
	3	38	57.6	0	0
Constipation	Y	51	77.3	16	40
	Ν	15	22.7	24	60
Sedentary	Y	50	75.8	40	100
lifestyle	Ν	16	24.2	0	0

Table 2. The basic statistical parameters for age and body mass index (BMI) and the results of t-test between males and females participants for experimental and control group. *- statistically significant at p<0.05

Group		Age			
		Х	SD	Min.	Max.
Experimental	F	45.9	13.1	27	68
	М	52.7	13.0	27	69
	All	48.2	13.4	27	69
	t			2.0	
	р		0.0)475*	
Control	F	53.3	18.8	27.0	89.0
	М	48.5	16.7	25.0	78.0
	All	51.0	17.8	25.0	89.0
	t			0.9	
	р		0.3	3998	
Group			E	BMI	
		Х	SD	Min.	Max.
Experimental	F	27.3	2.4	22	33
	М	27.9	3.1	24	35
	All	27.6	2.7	22	35

	t	0.9				
	р	0.3872				
Control	F	24.7	4.6	18.0	37.9	
	М	26.5	3.2	22.1	34.7	
	All	25.6 4.1 18.0 37.9				
	t	1.4				
	р	0.1601				

The patients with the highest value of overall subjective discomfort (rate 8 and 9) had the highest values of BMI (29.3 \pm 3.5) while those with mean value of the overall subjective discomfort 5 had BMI 23.5 \pm 0.2. The patients that rated their overall subjective discomfort with 8 and 9 all suffered from constipation. In the case of the degree of the hemorrhoidal disease the significant correlation was also obtained (R=0.62; p<0.0014) with sedentary lifestyle as the only statistically significant variable (0.0007).

Table 3. The results of multiple regression analysis testing for the correlation between the selected predictor variables and overall subjective discomfort and the degree of hemorrhoidal disease. *- statistically significant at p<0.05

Predictor	Experimental group					
variable	Overall su discor	Overall subjective discomfort		Overall subjective Degr discomfort		nemorrhoidal sease
	β	р	β	р		
Age	0.11	0.4585	0.01	0.9321		
BMI	0.26	0.0447*	0.05	0.7210		
Constipation	0.25	0.0471*	0.09	0.5444		
Gender	0.09	0.4288	0.03	0.8257		
Sedentary lifestyle	0.08	0.5746	0.55	0.0007*		
	R=0.63; p<0.0009*		R=0.62; p<0.0014*			
Predictor		Contro	l group			
variable	Overall su discor	lbjective nfort	Degree of hemorrhoidal disease			
	β	р	β	р		
Age	0.04	0.6132	0.01	0.8767		
BMI	0.21	0.0230*	0.22	0.0244*		
Constipation	0.46	0.0000*	0.43	0.0000*		
Gender	0.07	0.4044	0.10	0.2618		
Sedentary lifestyle	0.32	0.0004*	0.20	0.0304*		
	R=0.68; p∢	<0.0000*	R=0.64;	p<0.0000*		

Although, the age of the patients did not show significant contribution, the increase of the mean value of overall subjective discomfort with age was obvious. The patients rated their overall subjective discomfort as 5 belong to the age group of 33±5.7 years while those with rate 8 belong to the age group of 52±14.3 years. The lack of statistical significance could be attributed with high interpersonal differences. Johanson et al., 1990 reported that the incidence of hemorrhoidal disease increased with the age of the patients of both genders.)The results obtained by multiple regression analysis were completely in agreement with those obtained by general regression model expressed as Pareto charts of t-value confirming BMI and constipation as the only variables with statistically significant influence to the overall subjective discomfort of hemorrhoidal disease. When the grade of the hemorrhoidal disease was considered, the sedentary lifestyle was the only statistically significant predictor variable. Indeed, among 38 patients from the experimental group with third degree hemorrhoids 36 of them reported sedentary lifestyle while among those with second degree hemorrhoids sedentary lifestyle was reported by 13 of 28 patients. Those results were in agreement with previous research confirming that sedentary lifestyle and chronic

constipation represent significant risk factors in the development of hemorrhoidal disease (Riss et al., 2012).

The control group consisted of 21 females ranging from 27 to 89 years (53.3 ± 18.8) and 19 males ranging from 25 to 78 years (48.5 ± 16.7) (Tables 1 and 2). Among them 36 participants had 1st degree hemorrhoidal disease and four of them 2nd degree disease (Table 1)

40% of the patients suffered from constipation while all the participants reported sedentary lifestyle. BMI ranged (Table 2) from 18 to 37.9 (25.6 \pm 4.1). There was no significant difference in age or BMI between males and females.

Multiple regression analysis showed good, statistically significant correlation between selected predictor variables and both overall subjective discomfort (R=0.68; p<0.0000*) and the degree of the hemorrhoidal disease (R=0.64; p<0.0000). The predictor variables with the most, statistically significant contribution to the correlations were constipation, BMI and sedentary lifestyle (Table 3). Based on the results of Pareto charts of t-values it was obvious that constipation contributed the most to both overall subjective discomfort as well as the grade of the hemorrhoidal disease while the sedentary lifestyle and BMI were other two significant predictor variables. The patients with constipation showed higher scores for all five symptoms of the hemorrhoidal disease. The symptoms also increased with BMI. Similar to the experimental group the scores for all five symptoms increased with age of the patient and the highest values were obtained in the oldest group.

The Treatment Efficiency Experimental group

Before the therapy the mean values and standard deviations for pain, defecation discomfort, bleeding, itching and overall subjective discomfort were 6.6 ± 0.9 , 6.9 ± 1.0 , 2.2 ± 0.7 , 2.6 ± 0.6 and 7.0 ± 0.8 , respectively (Table 4). The pain and defecation discomfort values were slightly but insignificantly higher in male compared to female patients. The values of the variables bleeding severity and overall subjective discomfort were slightly but significantly higher in males and anal itching in female patients. A significant decrease of all five parameters was obtained after only three days of the treatment with the mean values and standard deviations of 2.2 ± 0.8 , 2.5 ± 1.0 , 0.6 ± 0.5 , 1.3 ± 0.7 and 3.0 ± 0.8 for pain, defecation discomfort, bleeding, itching and overall subjective discomfort, respectively.

All five variables were significantly lower compared to the baseline values. When comparing male and female participants a significant difference was observed for all five variables. The mean values for pain, anal itching and overall subjective discomfort were lower in male's subgroup and other two parameters in female's subgroup.

Table 4. Mean vales 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. a,b,c,d- significant difference between the pairs of the groups p<0.05

Gender	Both genders				
Group	0 (a)	3 (b)	5 (c)	10 (d)	
Pain	6.6±0.9 b,c,d	2.2±0.8 a,c,d	0.5±0.6 a,b,d	0.0±0.0 a,b	
Defecation	6.9±1.0	2.5±1.0	0.9±0.7	0.0±0.0 a,b,c	
discomfort	b,c,d	a,c,d	a,b,d		
Bleeding	2.2±0.7	0.6±0.5	0.0±0.0	0.0±0.0 a,b	
severity	b,c,d	a,c,d	a,b,d		
Anal itching	2.6±0.6	1.3±0.7	0.6±0.6	0.0±0.0 a,b	
severity	b,c,d	a,c,d	a,b,d		
Overall subjective	7.0±0.8	3.0±0.8	1.4±1.1	0.0±0.0 a,b,c	
discomfort	b,c,d	a,c,d	a,b,d		

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Gender		Fe	males	
Group	0 (a)	0 (a)	0 (a)	10 (d)
Pain	6.5±0.9	2.3±0.9	0.5±0.6	0.0±0.0 a,b
	b,c,d	a,c,d	a,b,d	
Defecation	6.9±1.0	2.5±1.1	0.8±0.6	0.0±0.0 a,b,c
discomfort	b,c,d	a,c,d	a,b,d	
Bleeding severity	2.1±0.6	0.6±0.5	0.0±0.0	0.0±0.0 a,b
	b,c,d	a,c,d	a,b,d	
Anal itching	2.8±0.6	1.4±0.6	0.6±0.5	0.0±0.0 a,b,c
severity	b,c,d	a,c,d	a,b,d	
Overall subjective	6.9±0.9	3.1±0.8	1.2±1.0	0.0±0.0 a,b,c
discomfort	b,c,d	a,c,d	a,b,d	
Gender		N	Aales	
Group	0 (a)	0 (a)	0 (a)	0 (a)
Pain	6.6±0.9	2.1±0.7	0.4±0.5	0.0±0.0 a,b
	b,c,d	a,c,d	a,b,d	
Defecation	7.0±1.0	2.6±0.9	1.0±0.7	0.0±0.0 a,b,c
discomfort	b,c,d	a,c,d	a,b,d	
Bleeding severity	2.3±0.8	0.7±0.6	0.0±0.0	0.0±0.0 a,b
	b,c,d	a,c,d	a,b,d	
Anal itching	2.3±0.4	1.0±0.7	0.6±0.6	0.0±0.0 a,b,c
severity	b,c,d	a,c,d	a,b,d	
Overall subjective	7.2±0.6	2.8±0.7	1.9±1.2	0.0±0.0 a,b,c
discomfort	b,c,d	a,c,d	a,b,d	

After five days of the therapy, there was no bleeding while the mean value and standard deviation were 0.5 ± 0.6 , 0.9 ± 0.7 , 0.6 ± 0.6 and 1.4 ± 1.1 for pain, defecation discomfort, itching and overall subjective discomfort, respectively. The mean value for pain was significantly lower in male's population while the values of defecation discomfort and overall subjective symptoms were significantly lower in female's subgroup. At 10th day of the treatment all five parameters were graded 0 by all 66 patients. No side-effects were reported in any of the patient.

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 support recuperation of the damaged mucosa by optimizing wound pH (Alam et al., 2014). Besides, osmotic effect of sugars creates the environment unfavorable for pathogens growth that also helps in the recovery process. Beeswax provides excellent protective coating which prevents the contact between stool and the damaged mucosa and prevents further irritation and infection of the damaged area. The presence of glycerol and honey increased lubrication which resulted in the reduction of pain and discomfort during defecation.

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). The coagulation of the surface proteins resulted in the reduction of bleeding, shrinkage of the hemorrhoids and the formation of the protective coating over damaged tissue. For that purpose oil macerates of the plants: 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. The macerates of marigold flowers (Calendula officinalis L.) and chamomile flowers (Matricaria chamomilla L.) were used due to its soothing and calming effect as well as their strong antiinflammatory and wound healing activity (Orescanin, 2016). In addition to above mentioned beneficial effects, oil macerates and essential oils also served as the natural preservatives and malodor correctors. Recent study (Oreščanin, 2017) investigated the efficacy of multi-herbal ointment consisted of the macerates of the plants S. officinale, P. major, C. officinalis, S. officinalis, H. perforatum, A. millefolium, P. aviculare, B. perennis, Q. robur, O. europaea, U. dioica, Capsella bursa-

pastoris, M. chamomilla; essential oils M. alternifolia, C. martini, O. vulgare, E. caryophyllata, T. vulgaris ct. thymol, C. camphora ct. cineol; Cera alba; honey and glycerol for the treatment of external hemorrhoids during 10 consecutive days. Before the treatment the mean values and standard deviations for pain, defecation discomfort, bleeding, itching and overall subjective discomfort were 7.2±0.8, 7.6±0.5, 2.7±0.7, 2.6±0.8 and 7.7±0.5, respectively. A significant decrease of all five parameters was obtained after only three days of the treatment with mean values of 3.2, 3.4, 0.7, 0.9 and 2.9 for pain, defecation discomfort, bleeding, itching and overall subjective discomfort, respectively while at 10th day of the treatment all five parameters were graded 0 by all treated patients. No side-effects were observed in any of the patient. It was concluded that the treatment outcome could be linked with the herbal composition with proven astringent, vasoconstrictor, haemostatic, anti-inflammatory and wound healing potential. Noori 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 anal fissure or hemorrhoids. The ointment significantly reduced bleeding and relieved itching and pain in the patients with hemorrhoids. The initial values of the scores for pain, bleeding and itching were reduced from 2.77 \pm 2.07, 1.6 \pm 0.69 and 1.57 \pm 0.78, respectively to 0, 0.2 \pm 0.42 and 0 after four weeks of the treatment. In the case of the patients with anal fissure the scores for pain, bleeding and itching reduced from initial values 6 ± 1.58 , 2.2 ± 0.83 and 1.5 ± 0.57 , respectively to 0 in the end of the therapy for all three symptoms. 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.

The results obtained in the present study are in the range with previously published data.

Control group

Before the therapy the mean values and standard deviations for the variables pain, defecation discomfort, bleeding severity, anal itching and overall subjective discomfort were 4.0 ± 1.1 , 4.0 ± 0.9 , 0.8 ± 0.6 , 3.6 ± 1.1 and 3.8 ± 1.0 , respectively (Table 5). There was no significant difference between males and females for neither of the mentioned variable.

Following three days of the therapy all five variables showed statistically significant decrease of their mean values that dropped to 2.5 ± 1.2 , 2.4 ± 1.1 , 0.3 ± 0.4 , 1.9 ± 1.1 and 2.4 ± 1.1 for pain, defecation discomfort, bleeding severity, anal itching and overall subjective discomfort, respectively. There was no significant difference in the treatment efficiency between male and female population. By increasing the treatment time to five days the values of all five variables showed further decrease and reached the values of 1.8 ± 1.0 , 1.6 ± 1.1 , 0.0 ± 0.2 , 0.8 ± 0.7 and 1.5 ± 0.9 for pain, defecation discomfort, bleeding severity, anal itching and overall subjective discomfort, prespectively.

Table 5. Mean vales 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 Faktu anti hemorrhoidal ointment. a,b,c,d - significant difference between the pairs of the groups p<0.05

Gender	Both genders			
Group	0 (a)	3 (b)	5 (c)	10 (d)
Pain	4.0±1.1 b,c,d	2.5±1.2 a,c,d	1.8±1.0 a,b,d	1.0±0.8 a,b,c
Defecation discomfort	4.0±0.9 b,c,d	2.4±1.1 a,c,d	1.6±1.1 a,b,d	0.9±0.7 a,b,c
Bleeding severity	0.8±0.6 b,c,d	0.3±0.4 a,c,d	0.1±0.3 a	0.0±0.2 a
Anal itching severity	3.6±1.1 b,c,d	1.9±1.1 a,c,d	1.3±0.9 a,b,d	0.8±0.7 a,b,c

Overall subjective	3.8±1.0	2.4±1.1	1.5±0.9	0.9±0.9 a,b,c
discomfort	b,c,d	a,c,d	a,b,d	
Gender		Fe	males	
Group	0 (a)	0 (a)	0 (a)	10 (d)
Pain	4.0±1.4 b,c,d	4.0±1.4 b,c,d	4.0±1.4 b,c,d	1.0±0.8 a,b,c
Defecation discomfort	4.0±1.0 b,c,d	4.0±1.0 b,c,d	4.0±1.0 b,c,d	0.9±0.7 a,b,c
Bleeding severity	0.7±0.6 b,c,d	0.7±0.6 b,c,d	0.7±0.6 b,c,d	0.0±0.2 a
Anal itching severity	3.6±1.3 b,c,d	3.6±1.3 b,c,d	3.6±1.3 b,c,d	0.8±0.7 a,b,c
Overall subjective discomfort	4.0±1.1 b,c,d	4.0±1.1 b,c,d	4.0±1.1 b,c,d	0.9±0.9 a,b,c
Gender		N	Aales	
Group	0 (a)	0 (a)	0 (a)	0 (a)
Pain	4.0±0.8 b,c,d	4.0±0.8 b,c,d	4.0±0.8 b,c,d	4.0±0.8 b,c,d
Defecation discomfort	3.9±0.8 b,c,d	3.9±0.8 b,c,d	3.9±0.8 b,c,d	3.9±0.8 b,c,d
Bleeding severity	0.9±0.5 b,c,d	0.9±0.5 b,c,d	0.9±0.5 b,c,d	0.9±0.5 b,c,d
Anal itching severity	3.5±0.8 b,c,d	3.5±0.8 b,c,d	3.5±0.8 b,c,d	3.5±0.8 b,c,d
Overall subjective discomfort	3.7±0.8 b,c,d	3.7±0.8 b,c,d	3.7±0.8 b,c,d	3.7±0.8 b,c,d

Finally, on tenth day of the treatment the values dropped to 1.0 ± 0.8 , 0.9 ± 0.7 , 0.0 ± 0.2 , 0.8 ± 0.7 and 0.9 ± 0.9 for pain, defecation discomfort, bleeding severity, anal itching and overall subjective discomfort, respectively. Newman-Keuls test showed no significant difference between males and females for neither of the treatment time. When both genders were considered a significant difference was observed among all treatment periods for all tested variables with the exception of bleeding severity between 3rd and 5th day as well as between 5th and 10th day.

CONCLUSION

Both Bioapifit and Faktu ointment showed significant decrease of the symptoms of hemorrhoidal disease during the treatment period. Bioapifit ointment showed significantly higher decrease of all symptoms for each treatment period compared to the Faktu ointment. Presented results revealed that the preparation combining honeybee's products with herbal ingredients could be used safely and effectively for the treatment of the symptoms of hemorrhoidal disease. The combination of the ingredients with soothing, calming, coating, pH adjusting, lubricating and antiinflammatory effect with those with proven astringent, vasoconstrictor and haemostatic activity resulted in alleviation followed by complete disappearance of the symptoms like pain, bleeding, itching and defecation discomfort.

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