Original Communication

Alpha Lipoic Acid Reduces Symptoms and Inflammation Biomarkers in Patients with Chronic Hemorrhoidal Illness

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Abstract: *Background:* Oral dietary supplementation is becoming increasingly popular as an addition to classical approaches for the prevention and treatment of hemorrhoidal disease. *Aim*: To examine the effect of orally administrated alpha lipoic acid (ALA), known for its antioxidant and anti-inflammatory properties, in the treatment of patients with permanent symptoms of hemorrhoidal disease. *Methods:* Patients with second- and third-degree hemorrhoids (n = 100) were enrolled into a randomized, open label, single-center trial. The study group (n = 50) was treated with 200 mg of orally administered ALA once a day during the 12-week period, the control group (n = 50) did not receive any treatment. *Results:* There were no significant differences in demographics, diagnosis, or exposure to major risk factors between the study and placebo group at baseline. ALA significantly improved subjective efficacy variables, such as pain and discomfort ($p < 0.01$) as well as objective signs of the disease, such as bleeding ($p < 0.01$), in comparison to the control group. Furthermore, the 3-month treatment significantly reduced the number of patients with positive C-reactive protein (CRP) value (serum CRP > 5 mg/L) from 18% before to only 2% after the treatment ($\chi^2 = 4.65$; $p < 0.01$). Average leukocyte count has also been significantly reduced in the treatment group ($p < 0.01$) from 7.29×10^9/L before to 6.18×10^9/L after treatment. *Conclusions:* The obtained results indicate that ALA is effective in the treatment of second- and third-degree hemorrhoids. Larger, double-blind controlled trials are needed to confirm the results and to investigate optimal treatment regimens.

Keywords: Alpha lipoic acid, anti-inflammatory effect, clinical study, hemorrhoids

Introduction

Alpha lipoic acid (ALA) is a coenzyme of multienzyme complexes, such as pyruvate dehydrogenase complex, catalyzing the decarboxylation of α-ketoacids, and is involved in the regulation of carbohydrate and lipid metabolism. Recently, ALA has been recognized as a potent antioxidant due to its free radical scavenging activity and involvement in the regeneration of active forms of other cellular antioxidants [1]. It is rapidly absorbed from the gastrointestinal tract and is primarily metabolized in the liver through mitochondrial β-oxidation [2]. However, it rapidly accumulates in liver, skeletal muscle, and heart, and it crosses the blood-brain barrier and accumulates in the cerebral cortex. ALA also does not exhibit any serious side effects and thus has a great potential for utilization as a dietary or therapeutic supplement under certain conditions [1]. Therefore, it has become a common ingredient in multivitamin formulas and anti-ageing supplements, while its principal use is in the treatment for diabetic neuropathy. Namely, oral ALA seems to reduce symptoms of peripheral neuropathy such as burning, pain or numbness and can lessen the damage of kidneys, heart, and small blood vessels [3]. Several recent studies proved its efficiency in promoting weight and fat loss, probably by stimulating the breakdown of fat and inhibiting formation of new fat cells [4, 5]. Current trials are investigating whether the above-mentioned beneficial properties of ALA make it an appropriate treatment for

the prevention of hypertension, inflammation, and vascular disease [6, 7]. Proposed mechanisms of action involve the antioxidant activity of ALA, mediated by its direct radical scavenging activity, regeneration of other antioxidants, and metal chelating activity [2]. ALA can also downregulate the activity of redox-sensitive transcription factor NFκB and thus reduce inflammation [8]. Its anti-inflammatory activity [9] and proven efficiency in improving vascular function [10, 11] might also make it suitable for and efficient in the treatment of hemorrhoidal symptoms.

Hemorrhoids (*noduli hemorrhoidales*) are the pillow-like clusters of veins and connective tissue that are situated beneath the mucus membranes in the lowest part of anus and rectum. Due to different risk factors that cause increased pressure in hemorrhoidal veins, they can become swollen and distended, causing the occurrence of a variety of characteristic symptoms such as *pruritus*, pain, anal discomfort, and bleeding [12–14]. Major risk factors for the occurrence of mentioned symptoms are infrequent and impaired defecation, diarrhea, genetic predisposition, poor diet, aging, prolonged sitting and lack of physical activity, anal infection, pregnancy, obesity, etc. [12, 13, 15]. The major findings of hemorrhoidal disease are abnormal dilatation and distortion of the vascular channel and destructive changes in the supporting connective tissue within, and, in some cases, inflammatory reaction and vascular hyperplasia [16]. Today hemorrhoids present an important public health problem, since they occur in half of the population over 50 years of age. At global level, the prevalence of hemorrhoidal symptoms has been estimated at 4.4% [15]. Therefore, finding new solutions and improvement of current options for the prevention and treatment of hemorrhoids is of great significance.

Usual treatment of hemorrhoidal disease requires an integrated approach that depends on the exact diagnosis, usually including diet modification and lifestyle changes combined with topical treatment (local anesthetics, corticosteroids, vasoconstrictors, antiseptics etc.). Such classical approach requires a high degree of patient compliance to be effective, and in case it fails, other non-surgical modalities can be used: rubber-band ligation, sclerotherapy, infrared coagulation, bipolar diathermy and direct-current electrotherapy, cryotherapy, laser therapy etc. Since these treatment options are rather costly and uncomfortable, patients often tend to postpone evaluation until surgical intervention is necessary. Therefore, oral dietary supplementation presents an attractive addition to the prevention and traditional treatment of hemorrhoids. At the moment, the primary natural supplement used for treatment of hemorrhoids are bioflavonoids. Efficiency of citrus flavonoids diosmin and hesperidin in revealing hemorrhoidal symptoms has been proved with several placebo-controlled clinical trials [17–19]. Efficiency has also been shown for flavonoids from bilberry extract [20] and the semisynthetic bioflavonoids oxerutins [21, 22]. Extracts of *Cissus quadrangularis and Ginkgo biloba* have been proved effective, acceptable, and safe in the treatment of patients with acute hemorrhoidal attacks [23, 24]. Although the exact mechanism of the activity in the above-mentioned preparations has not been explained in detail, it is primarily attributed to their anti-inflammatory and venotonic effects. During inflammation, which is characteristic for acute hemorrhoidal attacks, increased consumption of oxygen occurs, resulting in production of superoxide radicals, hydrogen peroxide, hydroxyl radicals, and hydrochloric acid. Therefore, preparations rich in antioxidants have been developed recently for topical and systematic treatment of hemorrhoids [25, 26].

Taking into account that alpha lipoic acid might reduce inflammatory activities, attenuate free radical damage and improve vascular functionality, it was decided to investigate the effect of lipoic acid supplementation on inflammatory factors and the intensity of symptoms of hemorrhoidal disease in patients with the diagnosis of chronic hemorrhoidal illness. To the authors' knowledge, this is the first study on the therapeutic application of lipoic acid in the treatment of hemorrhoids.

Patients and methods

Study site

The study was conducted in the primary health care institution of the Health Center Tuzla, Bosnia and Herzegovina, from August 2013 to June 2014. The protocol of clinical research was reviewed and cleared by the Ethics Committee of the Primary Health Care Institution of the Health Center Tuzla. Prior to entering the trial, all patients were duly informed about their participation in the study and gave their written informed consent. The course of the study is presented in Figure 1.

Patients

Basic medical data about age, sex, type and degree of hemorrhoidal disease, occurrence of other diagnosis, medication, and consumption of dietary supplements were collected. Patients were of both sexes, aged between 30 and 60 years with permanent symptoms of hemorrhoidal disease (second- and third-degree; second-degree hemorrhoids: protruded on defecation but reduced spontaneously; third-degree hemorrhoids: protruded on defecation but needed to be replaced digitally). Before admittance to the study, all patients underwent a proctology

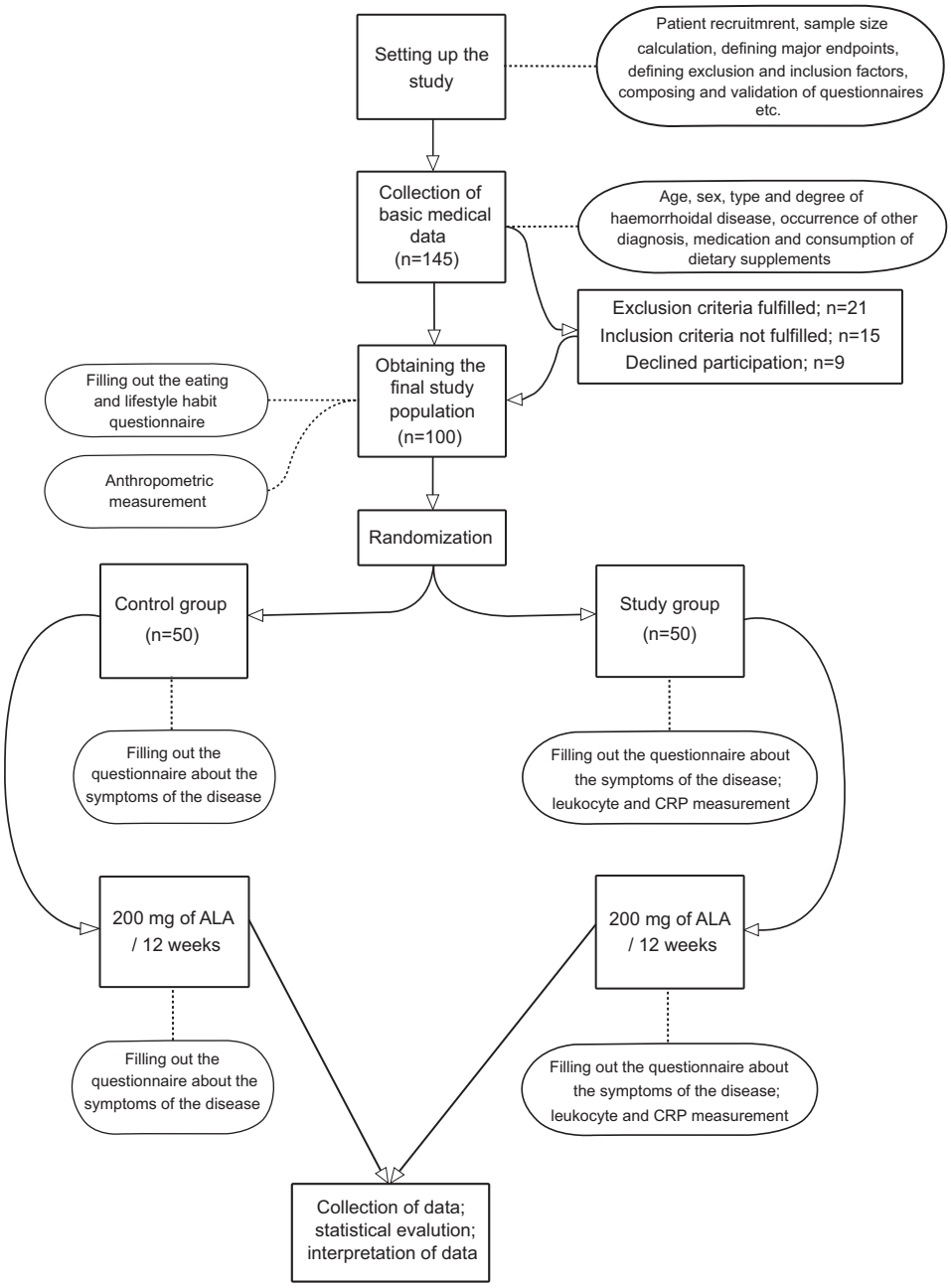

Figure 1. Flowchart of the study.

examination to exclude other associated proctologic diseases. Patients with fourth-degree hemorrhoids (continuously protruding) were excluded from the trial. Other exclusion factors were: tumors of the anus and rectum, perianal abscesses, perianal fistula, anal fissure, anal warts, sexually transmitted diseases of the anus, earlier surgery of the anus and rectum, and use of dietary supplements.

In total, 109 subjects fulfilled the selection criteria; however, 9 of them refused to take part in the study. At the beginning of the study all participants (100 patients) were asked to fill out the eating and lifestyle habit questionnaire that has been developed based on the recommendations and guidelines of the World Health Organization [27], Food and Agricultural Organization of the United Nations, Food and Agricultural Organization [28] and Codex Alimentarius Commission [29]. Validation and reliability of questionnaire have been evaluated by a panel of experts; validity has been checked in terms of content and construct validity. Reliability of the questionnaire has been evaluated in terms of stability (by test-retest method) and consistency (split-half method). The questionnaire mainly focused on the consumption of fruits and vegetables, duration of sitting and

physical activity and consumption of alcohol and cigarettes, since those are considered to be the main nutrition/lifestyle factors associated with the occurrence of hemorrhoidal disease [30]. Anthropometric measurements were conducted using standardized techniques. Weight was determined using an electronic digital scale measuring to the nearest 100 g. For height measurements patients wore no shoes, stood on a flat surface looking directly forward, with the line of vision horizontal and the chin parallel to the deck. A portable stadiometer (Seca, Chino, CA USA) was used for this purpose and height was measured to the nearest 0.1 cm. Obtained results were used for the calculation of body mass index.

Randomization and study protocol

Patients were randomly allocated to the study (n = 50) or the control group (n = 50). Taking into account the relatively small number of patients included in this study, a baseline adaptive randomization method (biased coin method) has been used. Balance was established for six baseline characteristics by adaptive randomization (age, sex, hemorrhoid stage, physical activity, fruit and vegetable consumption, and alcohol consumption). For sample size calculation Raosoft sample size calculator was used (Raosoft, Seattle, WA, USA), acceptable error set to 5%.

Patients in the study group received 200 mg of ALA in the form of film-coated pills, once a day, before a meal, for 12 weeks, while patients in the control group did not receive any treatment. All patients included in the study used the usual topical therapy in form of creams and ointments and periodically took oral analgesics. Participants were asked to maintain the same eating habits and lifestyle as before the study. Patients in both groups were asked to fill out a questionnaire about the symptoms of the disease at the beginning (0 weeks) and at the end of the trial (12 weeks). Prior to questionnaire administration, participants were given instructions on how to fill out the questionnaire completely and truthfully.

Estimation of the severity of hemorrhoidal symptoms

A special questionnaire about the symptoms of the disease has been created for conducting the study. Three most prominent symptoms in this disease have been used: the feeling of pain with bowel movements, feeling itchy in the anal area (*pruritus ani*), and the appearance of blood in the anal part of the intestine. The questionnaire contained the Wong-Baker FACES Pain Rating Scale [31] with verbal and pictorial descriptions of the level of pain. For the description of symptom intensity, a verbal scale has been used: no symptoms (0), mild symptoms (1), moderately strong (2), strong (3), extremely strong (4), and unbearably (5) pronounced symptoms of the disease. Pictorial descriptions were assigned to each level of pain in the questionnaire in order to contribute to a better understanding of the scale and make it suitable for use by older people. Based on the pain scale, the scale for symptoms has been created [32]. The appearance of blood in the anal area was described as no blood (0), traces of blood on toilet paper (1), a lot of blood on toilet paper (2), blood in the stool (3), blood in the toilet (4) and appearance of bleeding regardless of defecation (5).

Laboratory assessment

Biochemical inflammation markers monitored in patients, before and after taking the supplement, were C-reactive protein (CRP) and total leukocytes. Serum C-reactive protein concentrations were estimated by the semi-quantitative CRP-latex slide test (Linear Chemicals, Barcelona, Spain). The principle of this test is based on the immunological reaction between CRP as an antigen and the corresponding antibody coated on the surface of biologically inert latex particles [33]. The test belongs to the so-called rapid tests, since the results are obtained within 3 min. The results were expressed as negative (serum CRP < 5 mg/L) or positive (serum CRP > 5 mg/L).

Total leukocyte count was determined using a standard Turk chamber procedure [34]. Basically, the whole blood was diluted with Turk's solution (Merck, Darmstadt, Germany), which caused lysis of red blood cells, while leukocytes remained intact. The chambers (Electron Microscopy Sciences, Hatfield, PA, USA) were charged with adequately diluted processed blood; white blood cells were identified, and their distribution checked under the low-power objective. After counting white blood cells, total leukocyte count was calculated, taking into account the dilution factor.

Compliance

To ensure patients' compliance, each patient was provided with a known number of tablets. Patients were instructed to return the unused tablets at the end of the study. Degree of compliance was determined based on the number of returned tablets by each patient.

Statistical analysis

Data were analyzed using SPSS 17.0 for Windows (IBM, Armonk, NY, USA). All statistical tests were considered significant at the 0.05 probability level. The normality of variable distribution was determined by Kolmogorov-Smirnov

test and equality of variance was checked by Levene's test. Data were expressed as: mean ± standard deviation for all ratio variables and absolute frequencies for all categorical variables. An independent t-test analysis (ratio variables) and chi-squared test (categorical variables) were performed to ascertain whether significant differences existed between the patients in the experimental and the control group at baseline. The effect of the supplementation was assessed by Wilcoxon test, which is a nonparametric version of t-test for dependent samples.

Results

Patients

40 men and 60 women from Tuzla County, Bosnia and Herzegovina, diagnosed with permanent symptoms of stage-II and stage-III hemorrhoids, were included in the study. Age, sex, and lifestyle data of the control and of the study group are presented in Table I.

Analysis of nutrition and lifestyle habit data obtained from questionnaires showed that engagement of patients in physical activity was rather low: the majority of patients (77%) included in the study spent 2–8 h a day sitting, 52% of participants spent 30 min to 1 h a week walking and only 5% of participants were involved in regular (everyday) exercise. More than half of the patients in both the study and the control group were either overweight or obese. Consumption of alcohol was low among investigated patients: 94% of participants consumed alcohol rarely (34%) or never (60%). Half of participants were smokers and the average number of smoked cigarettes was 10–20/day. Since fiber consumption is also an important factor in the etiology and occurrence of hemorrhoidal disease, daily intake of fruit and vegetables has also been estimated. 62% of patients included in the study consumed one portion of vegetables/day, 29% of patients consumed 2–5 portions of vegetables/day. Consumption of fruit was more satisfactory; 45% of patients consumed one portion of fruit/day; 47% of participants consumed 2–5 portions of fruit/day.

Efficacy assessment

Patients' compliance to the 12-week supplementation with ALA, based on the amount of returned unused pills, was very satisfactory: over 90%. The effectiveness of supplementation on the severity of hemorrhoidal symptoms has been estimated by comparing the results obtained for the study and the control group before and after the treatment (Table II, Figure 2).

A mixed between-within subject's analysis of variance was conducted to assess the impact of group membership (control group, experimental group) on participants' scores on observed parameters (anal pain while sitting, anal pain at defecation, *pruritus ani,* and bleeding) across two-time periods (pre-intervention, post-intervention).

For all observed parameters there was a significant interaction between group type and time (anal pain while sitting: Wilks's lambda = 0.469, F (1, 98) = 111,06, p = 0.0001, partial eta squared = 0.531; for anal pain at defecation: Wilks's lambda = 0.485, F (1, 98) = 104.27, p = 0.0001, partial eta squared = 0.515; for *pruritus ani*: Wilks's lambda = 0.727, F (1, 98) = 36,89, p = 0.0001, partial eta squared = 0.273; for bleeding: Wilks's lambda = 0.722, F (1, 98) = 37.72, p = 0.0001, partial eta squared = 0.278), showing a reduction in observed scores across two time periods. For anal pain while sitting, anal pain at defecation, and bleeding, the main effect comparing the two groups was significant (for anal pain while sitting F (1, 98) = 8.820, p = 0.002, partial eta squared = 0.090; for anal pain at defecation F (1, 98) = 6.845, p = 0.019, partial eta squared = 0.055; for bleeding,

Table I. Age, sex, and lifestyle data of the control and study group.

Parameter	Study group (n = 50)	Control group (n = 50)	Group difference (t or χ^2)
Age (average)	52.28 ± 11.78	52.42 ± 9.71	−0.645; p > 0.05
Sex (m/f)	16/34	24/26	2.66; p > 0.05
BMI (underweight/normal/overweight/obese)	3/14/22/11	0/18/22/10	3.35; p > 0.05
Hemorrhoid stage (stage II/stage III)*	25/25	25/25	
Sitting (1–2/2–3/3–5/5–8/> 8 h a day)	1/19/8/11/11	6/24/10/5/5	8.88; p > 0.05
Physical activity (h/week) (sitting/walking 30 min/ walking 1 h/walking >1 h/regular exercise)	8/14/12/14/2	4/12/14/17/3	3.53; p > 0.05
Smoking (yes/no)	29/21	20/30	3.24; p > 0.05
Fruit consumption (0/once a day/2–5 times a day/more)	0/25/21/4	1/20/26/3	2.23; p > 0.05
Vegetable consumption (0/once a day/2–5 times a day/more)	3/35/10/2	3/27/19/1	4.16, p > 0.05
Alcohol consumption (every day/often/rare/never)	0/6/18/26	0/0/16/34	7.18; p > 0.05

*Stage-II hemorrhoids: hemorrhoids-protruded on defecation but reduced spontaneously; stage-III hemorrhoids: protruded on defecation but needed to be replaced digitally.

Table II. Impact of ALA supplementation on subjective efficacy variables (anal pain and discomfort).

	Study group (n = 50) *average ± stdev*	Control group (n = 50) *average ± stdev*
Anal pain* (while sitting)		
Before ALA	2.66 ± 0.82	1.62 ± 0.73
After ALA	1.46 ± 0.61	1.66 ± 0.77
Wilcoxon test, p	Z = −6.12; p < 0.01	Z = −0.587; p > 0.05
Anal pain* (at defecation)		
Before ALA	3.02 ± 1.12	1.94 ± 0.65
After ALA	1.7 ± 0.79	2.04 ± 0.78
Wilcoxon test, p	Z = −6.15; p < 0.01	Z = −1.311; p > 0.05
Pruritus ani*		
Before ALA	2.22 ± 1.00	1.90 ± 0.68
After ALA	1.34 ± 0.52	2.00 ± 0.81
Wilcoxon test, p	Z = −5,30; p < 0.01	Z = −0.832; p > 0.05
Bleeding*		
Before ALA	2.28 ± 1.49	1.22 ± 0.42
After ALA	1.26 ± 0.60	1.32 ± 0.59
Wilcoxon test, p	Z = −4.87; p < 0.01	Z = −1.890; p > 0.05

*The difference of efficiency of the tested approach between groups was significant; in all cases obtained p values were the same (p = 0.0001). The interaction between time and study group was also significant (for all observed parameters).

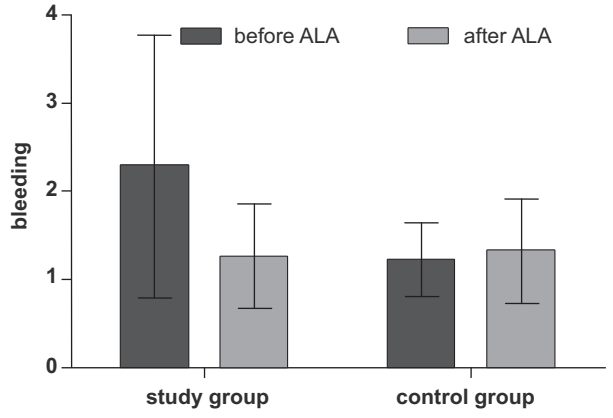

Figure 2. Impact of alpha lipoic acid on the appearance of blood in the anal area. Results are presented as means ± standard deviation. The appearance of blood in the anal area was described as no blood (0), traces of blood on toilet paper (1), a lot of blood on toilet paper (2), blood in the stool (3), blood in the toilet (4), and appearance of bleeding regardless of defecation (5). Columns marked with different letters belong to different statistical groups (p < 0.01).

F (1, 98) = 12.50, p = 0.001, partial eta squared = 0.102), suggesting differences in the effectiveness of approaches. As shown, all subjective efficiency variables (anal pain while sitting, anal pain at defecation and *pruritus*), as well as objective signs of illness (bleeding), were significantly reduced in the study group (p < 0.01) and remained unchanged in the control group (p > 0.05). To the authors' knowledge, this is the first time that ALA has been investigated and proved efficient in the treatment of hemorrhoidal symptoms. The exact mechanisms involved in efficiency of lipoic acid are not clear yet, but it is the authors' assumption that observed effects are at least partially associated to the anti-inflammatory efficiency of ALA, which has previously been shown crucial for its vascular-protective effects [1]. In order to assess potential anti-inflammatory effects of lipoic acid, initial total leukocyte count and CRP levels in study group were compared to the values obtained after 12 weeks of ALA supplementation (Figure 3).

Average leukocyte levels were normal before (7.29×10^9/L) and after supplementation (6.18×10^9/L), although significantly lower levels were determined after the treatment (p < 0.01). More importantly, the number of patients with elevated CRP levels was significantly reduced ($\chi^2 = 4.65$; p < 0.01): from 88.9% before treatment to 11.1% after treatment. Obtained results indicate that the efficiency of ALA in the treatment of the symptoms of hemorrhoidal disease might be mediated by its anti-inflammatory activity.

The results of the subgroup analysis of efficacy according to patients' age, sex, or BMI were consistent with the analysis of the total patient population. However, the limited number of patients in each subgroup precluded statistical evaluation of differences between subgroups.

Discussion

Conservative therapy for the prevention and treatment of hemorrhoids is primarily based on diet and lifestyle changes. As mentioned before, certain nutrition and lifestyle patterns present major risk factors for developing hemorrhoidal disease, and changes of these patterns

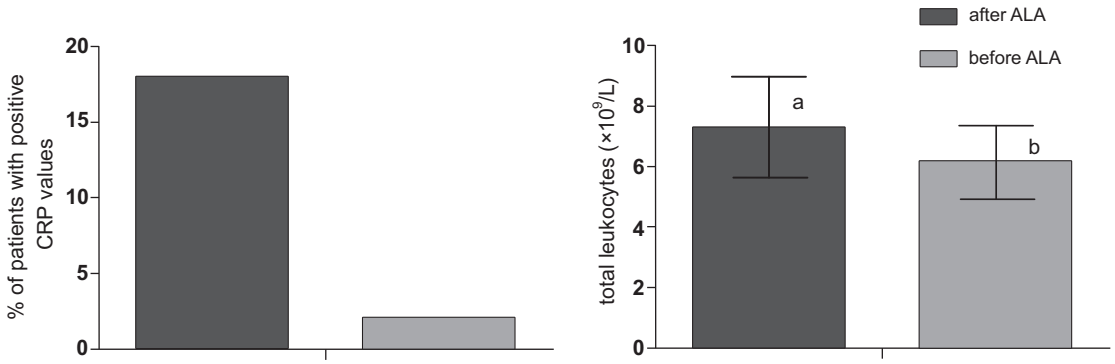

Figure 3. Impact of alpha lipoic acid on inflammation biomarkers, C-reactive protein (CRP) values and total leukocytes. *Total leukocytes are presented as means ± standard deviations. Columns marked with different letters belong to different statistical groups ($p < 0.01$).

promote healing and withdrawal of symptoms of the disease. The importance of mentioned risk factors has been reconfirmed by the results of our study; the majority of patients was overweight, practicing a sedentary lifestyle and consuming relatively low amounts of fibrous food (fruits and vegetables). Although effective, conservative treatment approaches based on the long-term changes of nutrition patterns require a high degree of patient compliance to be effective. Otherwise, topical preparations for relieving symptoms or different non-surgical modalities are prescribed. In case a non-surgical approach fails, the patient is usually referred to a surgeon [35].

In order to improve the effectiveness of conservative therapy and to avoid the need for uncomfortable non-surgical treatments or surgery, oral dietary supplementation in the treatment of hemorrhoids is becoming increasingly popular. Our results show that ALA can be considered effective in relieving the symptoms of second- and third-degree hemorrhoids in patients with permanent symptoms of hemorrhoidal disease. Twelve-week treatment with ALA resulted in 45.1% reduction of anal pain, 43.7% reduction of pain at defecation and 39.6% reduction of anal itching. Bleeding was also significantly reduced (44.7%).

The observed efficiency of ALA in reducing hemorrhoidal symptoms might be explained by its metabolic role as an antioxidant and its involvement in signal transduction resulting in downregulation of certain inflammation parameters. Elevated levels of oxidative stress play an important role in chronic inflammation which is thought to provoke early vascular events and is an important part of the etiology of hemorrhoidal illness. The oxidized (LA) and reduced (DHLA) form of ALA create a potent redox couple that has a standard reduction potential of −0.32 V, which makes DHLA one of the most potent naturally occurring antioxidants [36]. Both forms are capable of scavenging radicals and hypochlorous acid, while LA also terminates singlet oxygen [37]. Both forms also chelate redox-active metals *in vitro* and *in vivo* [38], while LA acts as the inducer of endogenous antioxidants such as intracellular ascorbate and glutathione levels [39, 40]. As mentioned before, LA also suppresses iNOS (inducible nitric oxide synthase) and downregulates the activity of NF-kappaB, an important transcription factor that induces expression of many genes involved in inflammation and endothelial cell migration [41].

Having in mind the antioxidant and anti-inflammatory properties of ALA, it has been studied as the therapeutic agent that might mitigate oxidant production and oxidative damage in various models of inflammation [6]. Recently, Santos and co-workers (2015) showed that ALA prevents the ammonia-induced inflammatory response [42]. Chaudhary et al. (2006) showed that lipoic acid inhibits expression of ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) in CNS endothelial cells and prevents T cell migration into the spinal cord in experimental autoimmune encephalomyelitis [43]. ALA had a protective effect on both senile and postmenopausal inflammation-mediated osteoporosis in rats [44] and showed protection against ulcerative colitis and the associated systemic damage in mice [45].

Although numerous *in vitro* and animal studies confirmed the anti-inflammatory effect of ALA [6], it has rarely been investigated in humans. Recently, the ISLAND trial showed a significant 15-% decrease in serum interleukin-6 levels following 4 weeks of supplementation with ALA (300 mg/day) [11].

ALA has also been proved to beneficially affect the vascular system, by significantly increasing endothelium-dependent NO-mediated vasodilation [46]. Although the mechanism of the observed effect has not been completely explained, it probably includes eNOS activation as shown by Smith et al. (2003) [47]. Whereas supplementation with ALA has been proved effective in the prevention of diabetes complications, obesity, and atherosclerosis by several clinical trials [1], its effectiveness in relieving hemorrhoidal symptoms has not yet been investigated to the authors'

knowledge. Therefore, it is impossible to discuss results obtained in this study in relation to other available studies. However, observed efficiency of ALA was comparable to the efficiency of some other natural preparations used for treatment of hemorrhoids, such as short-term application of Ginkgo biloba-Troxerutin-Heptaminol Hce [24]. Similar effects were also noticed after 12-week application of Pilex combination therapy [48]. Results similar to ours were also described after 2–4 weeks of oral application of a novel antioxidant formula, where significant decrease in the degrees of hemorrhoids was noticed in comparison to the placebo group [49].

Our results indicate that the effectiveness of ALA in calming hemorrhoidal symptoms is at least partially associated with its anti-inflammatory activity. Namely, a 12-week treatment with alpha lipoic acid resulted in significant reduction of the number of patients with elevated CRP values. Such observations are consistent with recent literature data. For example, Manning et al. [50] showed that long-term treatment with ALA significantly reduced inflammation markers in patients with metabolic syndrome. Similarly, HsCRP values were significantly reduced after an 8-week supplementation with ALA in patients on hemodialysis [51].

The major limitation of our study presents the fact that in spite of randomization, the control group showed a significantly lower level of pain before the treatment in comparison to the study group. As presented in Table I, all other relevant factors (sex, gender, diagnosis, lifestyle habits) were the same for both investigated groups of patients ($p > 0.05$). The reason for the observed discrepancy is not clear to the authors; it was unexpected and coincidental and can be avoided in the future by increasing the number of patients in the study. Other weak points are the missing placebo and the missing blinded design, as well as the inclusion of only one inflammatory biomarker (CRP). However, considering the fact that this was, to the authors' knowledge, the first investigation of the effectiveness of ALA in the treatment of hemorrhoidal disease, the obtained results can be considered as a valuable contribution to the current knowledge about nutritional supplementation in hemorrhoidal disease. As mentioned before, due to randomization, treatment- and control group did not differ significantly in terms of demographics, diagnosis or exposure to major risk factors. However, the intensity of self-reported symptoms in the control group was significantly lower at baseline in comparison to the study group and it is considered to be the major limitation of our study. This anomaly can be avoided in future studies by increasing the number of patients and adding more objective markers to be determined during the clinic visit (proctorrhagia, proctitis, anal prolapse etc.), rather than the self-reported subjective efficacy variables when assessing treatment efficiency.

Conclusions

Permanent symptoms of hemorrhoidal disease are more frequent in overweight middle-aged and elderly patients, with inadequate amounts of fibers in their diet and low physical activity. A 12-week supplementation with 200 mg of ALA can significantly reduce the severity of pain and itching in the anal area, as well as the occurrence of bleeding in patients with stage-II and stage-III hemorrhoids. Significant reduction of serum levels of inflammation biomarkers (C-reactive protein and total leucocytes) has also been noticed in the treatment group. Larger, double-blind placebo-controlled studies are needed to provide additional knowledge on the effectiveness, dosage, and mechanisms of action of ALA in the treatment of hemorrhoidal disease.

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