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Journal

Gynecological Endocrinology ›

Volume 35, 2019 - Issue 9

PC-RCT: Alpha-Lipoic Acid at combination with Mefenamic Acid in primary Dysmenorrhea

Effect of alpha-lipoic acid at the combination with mefenamic acid in girls with primary dysmenorrhea: randomized, double-blind, placebo-controlled clinical trial

Mojgan Yousefi, Maria Kavianpour, Sepideh Hesami, Mohamadreza Rashidi Nooshabadi & **Hossein Khadem Haghighian**

Pages 782-786 | Received 27 Aug 2018, Accepted 01 Mar 2019, Published online: 07 Apr 2019

Download citation https://doi.org/10.1080/09513590.2019.1590544 Check for updates

Abstract

Primary dysmenorrhea is a common gynecologic disorder and is one of the main causes for referral to the gynecology clinic. This study aimed to determine the effects of alpha-lipoic acid (ALA) and mefenamic acid and a combination compared with placebo on the girls with primary dysmenorrhea. This double-blind, placebo-

l trial done on population consisted of female students living in

azvin University of Medical Sciences who had moderate to severe

dysmenorrhea using the Visual Analog Scale (VAS) questionnaire. Participants were randomly divided into four groups (n = 100): ALA, mefenamic acid, ALA + mefenamic acid and placebo groups. ALA and mefenamic acid were administrated in 600 mg and 250 mg, respectively. The severity of the pain was measured in the beginning and the end of the study. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). Our final results suggested that, although mefenamic acid significantly decreased the menstrual pain, ALA supplementation, 600 mg, would be more efficient than mefenamic acid in 250 mg. Also, the combination of ALA and mefenamic acid significantly has been far. Considering the ALA supplementation effect on pain relief in patients with primary dysmenorrhea, this antioxidant can be recommended for the healing of symptoms of these patients.

Trial registration: Iranian Registry of Clinical Trials identifier: IRCT20141025019669N8.

Chinese abstract

原发性痛经是一种常见的妇科疾病, 是转诊至妇科门诊的主要原因之一。本研究旨在确定α-硫辛酸（ALA）和甲芬那酸以及与安慰剂相比对原发性痛经女孩的影响。这项双盲、安慰剂对照临床试验针对人群是居住在加兹温医科大学宿舍的女学生, 并且视觉模拟量表（VAS）调查问卷得出中度至重度痛经。参与者被随机分为四组（n = 100）：ALA, 甲芬那酸, ALA+甲芬那酸, 安慰剂组。ALA和甲芬那酸分别给药600mg和250mg。在研究的开始和结束时测量疼痛的严重程度, 采用SPSS软件（SPSS Inc., Chicago, IL）进行统计学分析。我们的最终结果表明, 虽然甲芬那酸显著降低了经期疼痛, 但补充ALA 600mg比250mg甲芬那酸更有效。此外, ALA和甲芬那酸的结合更显著。考虑到ALA补充缓解原发性痛经患者疼痛的作用, 可推荐这种抗氧化剂来治疗这些患者的症状。

Keywords: Primary dysmenorrhea, alpha-lipoic acid, mefenamic acid, menstrual pain

Introduction

In this article

tion or dysmenorrhea is a common gynecologic disorder and is causes for referral to the gynecology clinic [1]. Dysmenorrhea is

classified into two primary and secondary types. Primary dysmenorrhea occurs in the absence of proven pathological problems, and secondary dysmenorrhea is due to underlying pelvic pathology such as pelvic inflammatory disease, congenital Müllerian anomalies, ovarian cysts organ pathology, endometriosis, or fibroids [2]. The symptoms of primary dysmenorrhea usually begin within a few hours or at the same time as menstrual bleeding begins, and a maximum of 48–72 h, and may be accompanied by symptoms such as a headache, dizziness, fever, nausea, vomiting, diarrhea, and fatigue [3]. Although dysmenorrhea is not life-threatening, it can have adverse effects on the quality of life and the mental status of individuals [4].

Although, there is not enough information to indicate the etiology of primary dysmenorrhea, a combination of factors including the increase of prostaglandin concentration, vasopressin, leukotrienes, uterine contractions with ischemia and psychosocial factors have been implicated in the development of primary dysmenorrhea [5]. The formation and excessive release of prostaglandins, especially prostaglandins E2 and F2a (which are secreted from the uterine endometrium during menstruation) is a hypothesis that has been confirmed more than other causes of primary dysmenorrhea due to its direct relationship with increased pain in menstruation [6]. A recent study suggested that acute inflammation has a main role in dysmenorrhea pain that can be measured by the inflammatory biomarkers. The authors proposed that anti-inflammatory factors can be helpful for remedy of these symptoms [7]. The initial treatment is drugs that inhibit prostaglandin production; non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen, naproxen, and mefenamic acid [8,9]. Although a series of research evidence supports the effectiveness of these drugs, they also have a number of side effects and restrictions, including that some people are not relieved of these therapeutic interventions [10]. Thus, alternative treatments such as herbal treatment and supplement treatment are under research to find safer medication compared to NSAIDS [11]. Alpha-lipoic acid (ALA) is a naturally occurring dithiol compound that is synthesized in the mitochondria. Only small amounts of LA can be obtained from the diet and therefore, most information on clinical effects comes from studies that supplementing ALA [12]. According to previous studies, ALA has

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vestigated as a therapeutic agent for several pathological pain
ding diabetic polyneuropathy [13], chemotherapy-induced

neuropathy, burning mouth syndrome, musculoskeletal pain (fibromyalgia pain), and carpal tunnel syndrome [14]. Therefore, this study designed to evaluate the ALA oral supplementation for decreasing the symptoms in women with dysmenorrhea.

Materials and methods

Study design

12b This study was conducted as a double-blind, placebo-controlled clinical trial. The research population consisted of female students living in dormitories of Qazvin University of Medical Sciences who had moderate to severe dysmenorrhea using the Visual Analog Scale (VAS) questionnaire [15]. The study was registered in the Iranian Registry of Clinical Trials website by the IRCTID: IRCT20141025019669N8 and protocol had approved by the Ethics Committee of the Qazvin University of Medical Sciences, Qazvin, Iran.

Inclusion and exclusion criteria

Inclusion criteria were as follows: single women with regular menstruation from 21 to 35 days, primary menstrual pain in most recent years, without significant pathology and body mass index (BMI) below 30. Exclusion criteria were as follows: history of abdominal or pelvic surgery, use of oral contraceptive pills (OCPs), having a history of women's illness, taking medications and sedation 4 h before the study, professional athlete, unusual consumption of salt or one of the food groups, taking antioxidants supplementation one year ago, having any symptoms, including stinging, itching, and discharge from the vagina, irregular menstrual periods, smoking, kidney disease, heart disease, diabetes, asthma, and hypothyroidism or hyperthyroidism.

Sample size calculation

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sample size, we used the pain intensity factor before and after the ch was used in Kashanian et al. study [16]. Thus, the mean and

standard deviation of the duration of pain intensity, before and after the supplementation were 7.47 ± 1.82 and 4.7 ± 1.8 for each group of 16 people. Considering the drop in participants during the study, 25 people were considered for each group.

$$N=[(Z1-\alpha/2+ Z1-\beta)\ 2\ (SD12+SD22)]/\Delta 2$$

$$Z1-\alpha/2=2.58,\ Z1-\beta=1.64, N=15$$

Data collection

The collection of demographic information and menarche onset, menstrual duration (day), interval between menstruation (day), duration of dysmenorrhea at each menstrual period (day and hour), and measurement of pain were measured using a questionnaire and the standard instrument of VAS, this tool is standard and its validity and reliability have been proven in various studies. In this study, participants were trained to indicate the severity of pain that would experience during the first, second, and third days of the menstrual cycle using the VAS. In this method, the classification was done according to the scores of the pain (mild: 0–3; moderate: 3.1–6; severe: 6.1–10).

Intervention

The sampling method was randomly selected from Dormitories of Qazvin University of Medical Sciences. At this stage, the volunteer students with primary dysmenorrhea were invited to participate in the project. Then, informed consent was completed among eligible individuals. The data collection tool was a questionnaire that was divided into three sections: demographic characteristics (e.g. age, BMI, and marital status); menstrual characteristics included: menarche age, menstrual duration (day), interval between menstruation (day), duration of dysmenorrhea in each menstrual period (day and hour) and pain intensity (by VAS).

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y measurement tool is a 10 cm ruler, the first and the last of which
umbers zero and 10 so that zero indicates the absence of pain

and 10 represents the most severe pain that one person may experience. This tool is standard and its validity and reliability have been proven in various studies. At the beginning of the study, individuals with primary dysmenorrhea, single, and willing to participate in the study, received written consent for supplementary care. Participants were randomly divided into four groups: ALA capsules, mefenamic acid capsules, ALA + mefenamic acid capsules, and placebo groups. The first group received a 600 mg capsule of ALA daily for five days (2 days before menstruation and three days after the onset of the course). The second group received a 250 mg capsule of mefenamic acid daily for five days, similar to the previous group. The third group received a single ALA capsule (600 mg)+one capsule of mefenamic acid (250 mg) daily for five days. The placebo group also received capsules similar to ALA. Patients were advised to avoid diet changes during the intervention. In order to control the confounding factors of diet, at the beginning and the end of the study, food intake was assessed using a nonconsecutive three-day dietary survey using a 24-h recall method (including two normal days and one day off).

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Statistical analysis

SPSS software v.17 was utilized as a data analyst (SPSS Inc., Chicago, IL). Due to the normal distribution of variables, which were checked by the Kolmogorov–Smirnov test, paired *t*-test is used to compare before and after supplementation in each group and one-way ANOVA was applied to compare four groups. The Mann–Whitney test was used in the absence of normal data. All data are presented as mean ± SD and statistically signification was defined as $p < .05$.

Result

Among 100 volunteered female students, three people were discontinued from the study for personal reasons. The final analysis was applied to 97 participants who completed the study (Figure 1).

ırt of patients' enrollment.

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The demographic and menstruation cycles' information of the participants is presented in Table 1. The groups were similar in terms of demographic and menstruation cycles' information characteristics. As shown in Table 1, no significant difference was observed in baseline characteristics.

Table 1. Comparison of characteristics between experimental and control groups.

CSV Display Table

As shown in Table 2, no statistically significant difference was found between the groups in terms of the average daily intake of calorie, macronutrients, and some micronutrients.

Table 2. Average daily intake of calorie, macronutrients and some micronutrients during the study.

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The severity of pain (as assessed by VAS) was classified into three categories, 0–3 = mild, 3.1–6 = moderate, and 6.1–10 = severe. A detailed classification of patients in each category is given in Table 3.

Table 3. Distribution of pain scores characteristic in experimental and control groups.

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The mean pain severity before treatment did not show a statistically significant difference between the four groups, but the comparison of intra-group variations of pain shows that it was reduced after treatment in the lipoic acid group ($p = .046$), mefenamic acid group ($p = .045$), and lipoic acid + mefenamic acid group ($p = .041$). There was no significant difference in placebo groups (Table 4).

Table 4. The comparison of pain intensity in baseline and end of the study in groups.

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Discussion

Primary dysmenorrhea remains a challenging condition to treat, with current recommended pharmacological therapies providing only partial relief from pain, and sometimes it causes other side effects. However, the main mechanism for treatment of dysmenorrhea is the prevention of prostaglandin synthesis and other chemical metabolites. Several types of PG synthesis inhibitors include aspirin, propionic acid derivatives (ibuprofen, naproxen, ketoprofen), and fenamates (mefenamic acid, meclofenamate, flufenamic acid) [17]. These drugs, with the mechanism of inhibiting cyclooxygenase, lead to significant reductions in PG production and subsequent reduction of PG concentration in the endometrial fluid and reduction of uterine tone [18].

The present study examined the efficacy of ALA supplementation on symptoms of primary dysmenorrhea compared to the mefenamic acid, ALA + mefenamic acid, and placebo for 8 weeks in female students with primary dysmenorrhea. Generally, in the different groups, the severity of pain was decreased after administration but this reduction was higher in the first two groups (ALA and ALA + mefenamic acid) than in the mefenamic acid group.

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ve been conducted previously on the health benefits of ALA and its ever, few studies have examined the effect of this component on

the symptoms of primary dysmenorrhea. For example, results of Ha et al. study showed that ALA inhibited PGE2 synthesis by inhibiting COX-2 activity. They investigated the effects of ALA on osteoclastic bone loss associated with inflammation. Their results showed that ALA inhibited the production of interleukin-1 induced prostaglandin, even in the presence of arachidonic acid, without effect on the expression of COX-2 and membrane-bound PGE2 synthase. Also, they stated that their results indicated the possibility that ALA could have beneficial effects on preventing several diseases mediated by PGE2 overproduction as well as osteoclastic bone loss associated with inflammation [19].

Previous studies have revealed that ALA provided antioxidant and anti-inflammatory activity and improved pain and paresthesia in patients with neuropathic pain syndrome, such as carpal tunnel syndrome [14], diabetic neuropathy [20], and burning mouth syndrome [21], musculoskeletal pain [22], bladder pain syndrome [23], and chemotherapy-induced neuropathy [24].

ALA acts by various mechanisms, it can be considered as a potent antioxidant through several mechanisms, including chelation of metal ions, scavenging of free radicals, and rehabilitation of endogenous and exogenous antioxidants, such as ubiquinone, vitamins C and E, and glutathione [25]. LA and DHLA can also be used as powerful anti-inflammatory through powerful scavenging activity, metabolic support of nerve cells and modulation of neurotropic cytokines release. All together, these mechanisms reduce inflammation, improve the functioning of the nerve fibers and promote neuroprotection and neuroregeneration [26]. Available data regarding the ALA supplementation on inflammatory markers showed that ALA administration decreases inflammatory markers such as CRP, IL-6, and TNF-α among patients with metabolic syndrome and related disorders [27–29]. ALA can also suppress inflammatory cytokines by activating serine kinases including IKKβ [30]. Zhang and Frei mentioned dose-dependently ALA inhibits NF-kB activation and adhesion molecule expression in human aortic endothelial cells [31]. It is expected that by regulating NF-kB/IkB signaling, the expression of many genes of NF-kB-dependent inflammatory factors such as IL-1 and IL-6, tissue factor, and TNF-α is

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ple cell types, such as lymphatic cells, monocytes, and endothelial
, is a potent and effective factor diminishing oxidative stress, with

neuroprotective and neurotrophic features [32].

Accumulation of reactive oxygen species results in the processing of the pain caused by the damage. For example, in a mouse pain model, levels of the endogenous antioxidant superoxide dismutase were associated with the level of capsaicin-induced hyperalgesia, such that lower antioxidant levels were connected with greater hyperalgesia [33]. In a randomized, placebo-controlled crossover study, conducted by Gilron et al. 24 adults with fibromyalgia, randomly allocated to two groups, ALA, and placebo. Participants were taken capsules containing 1800 mg/day ALA or placebo for 4 weeks followed by a 1-week washout followed by a second 4-week treatment and 1-week washout period. Primary outcome showed improvement in mean daily pain intensity (0–10) during week 4 of each period. Secondary outcomes, assessed during week 4 of each period, indicated improvement in global improvement, adverse events, mood, and quality of life [22]. The results of the meta-analytical study, Ziegler et al., in 2004, showed a significant improvement in neuropathic pain in over 1258 type 1 diabetic patient with polyneuropathy treated with an ALA injection of 600 mg per day for 3 weeks [34]. In 2006, Ziegler et al. performed a similar study with 600 mg ALA acid on 187 patients for 5 weeks, confirming the results of the previous study [35].

Conclusions

To the best of our knowledge, this proposed trial is the first to survey the efficacy of the antioxidant, ALA, for the treatment of dysmenorrhea. Our final results suggested that, although mefenamic acid significantly decreased the menstrual pain, ALA supplementation, 600 mg, would be more efficient than mefenamic acid in 250 mg. Also, the combination of ALA and mefenamic acid significantly has been far more effective. To obtain a complete picture of ALA treatment, it may be best to randomize a randomized clinical trial by measuring inflammatory factors such as PGE2 and PGF2 and more clinical trials with different doses and longer duration are suggested.

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Acknowledgements

The authors would like to thank all of the participants who completed the study protocol.

Disclosure statement

The authors declare that they have no conflict of interest.

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Funding

This work was financially supported by Research Affairs of Qazvin University of Medical Sciences, Qazvin, Iran with Grant number IR.QUMS.REC.1396.387.

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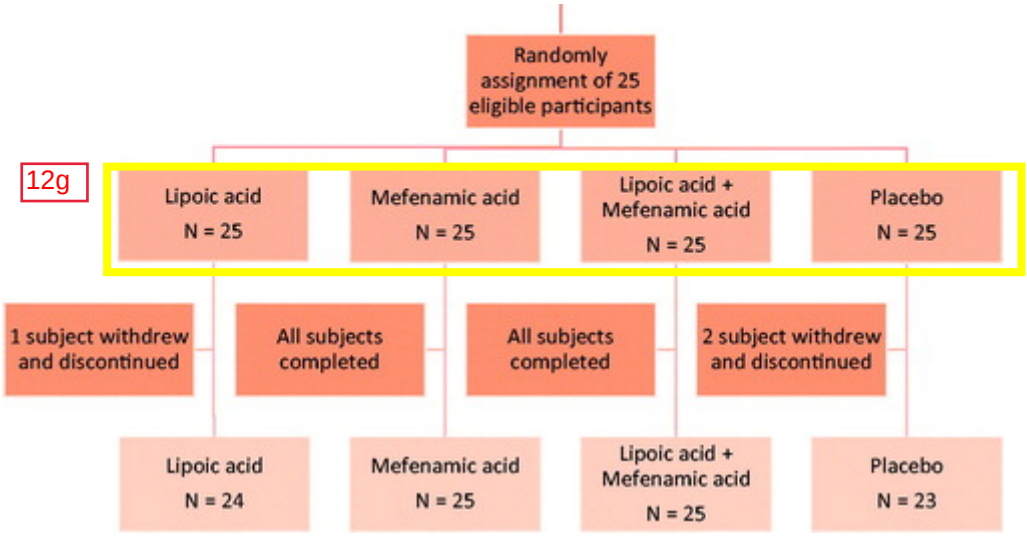
Pages 782-786 | Received 27 Aug 2018, Accepted 01 Mar 2019, Published online: 07 Apr 2019

Download citation https://doi.org/10.1080/09513590.2019.1590544 Check for updates

Figures & data

Figure 1. Flowchart of patients' enrollment.



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https://doi.org/10.1080/09513590.2019.1590544

PUBLISHED ONLINE:
07 April 2019

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Table 1. Comparison of characteristics between experimental and control groups.

Age (years, mean ± SD)	23.02 ± 2.17	22.49 ± 2.21	23.41 ± 3.08	23.11 ± 2.33	.674
Weight (kg, mean ± SD)	60.07 ± 9.11	59.19 ± 8.22	58.92 ± 8.08	60.23 ± 9.05	.701
Body mass index (kg/m^2, mean ± SD)	22.02 ± 2.17	21.87 ± 2.37	21.67 ± 2.19	22.11 ± 2.31	.726
Age at onset of menstruation (years, mean ± SD)	13.27 ± 1.13	13.48 ± 1.54	13.19 ± 1.42	13.61 ± 1.36	.902
Length of menstruation cycle (days, mean ± SD)	5.91 ± 1.08	6.09 ± 1.2	6.17 ± 1.01	6.3 ± 1.12	.918
Length of menstruation phase (days, mean ± SD)	27.19 ± 2.05	26.31 ± 2.24	26.42 ± 2.13	27.08 ± 2.14	.803

CSV

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Table 1. Comparison of characteristics between experimental and control groups.

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Table 2. Average daily intake of calorie, macronutrients and some micronutrients during the study.

Energy (kcal)	1708 ± 149.2	1695 ± 124.1	1640 ± 109.31	1725 ± 130.2	.642
Carbohydrate (g)	218.07 ± 11.3	210 ± 13.57	213.1 ± 16.17	209.04 ± 19.08	.513
Protein (g)	66.02 ± 6.4	63.19 ± 7	67.16 ± 6.31	62.39 ± 8.11	.831
Fat (g)	63.55 ± 8.62	66.91 ± 4.58	57.66 ± 2.15	71.04 ± 2.38	.325
PUFA(g)	20.01 ± 2.42	21.11 ± 3	17.6 ± 2.09	21.1 ± 2.8	.619
Vitamin C (mg)	66.18 ± 15.09	64.02 ± 7	63.39 ± 9.13	65.11 ± 8.26	.713
Vitamin E (IU)	6 ± 0.7	5.8 ± 0.11	5.67 ± 0.72	6.5 ± 0.6	.861
Selenium	116.34 ± 31.05	117.08 ± 30.8	116.6 ± 24.07	115.13 ± 21.4	.592

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Table 3. Distribution of pain scores characteristic in experimental and control groups.

Mild (0–3)	2 (8.3)	3 (12)	3 (12)	3 (13)
Moderate (3.1–6)	11 (45.8)	11 (44)	9 (36)	9 (39.1)
Severe (6.1–10)	11 (45.8)	11 (44)	13 (52)	11 (47.8)

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Table 4. The comparison of pain intensity in baseline and end of the study in groups.

Pain intensity	Before	7.12 ± 0.82	7 ± 1.01	7.61 ± 0.9	7.19 ± 1.07	.895
	After	5.42 ± 0.4**	6.01 ± 0.4**	4.3 ± 0.07**,†	7.06 ± 1.01	
	p Value*	.046	.045	.041	.803	

The data are expressed in mean ± SD.

**p* values refer to within-group differences at week 8 compared to baseline evaluated by paired *t*-test.

***p* values refer to differences between the intervention groups compared with the placebo group at week 8.

†*p* values refer to differences between the lipoic acid + mefenamic acid group compared with other intervention groups at week 8.

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