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Ameliorative Effect of Alpha Lipoic Acid on Endometriosis: An Experimental Model in Rats

Alfa Lipoik Asidin Endometriozis Üzerindeki İyileştirici Etkisi: Sıçanlarda Deneysel Model

Taylan Onat, Murat Çakır*

Yozgat Bozok University Faculty of Medicine, Department of Gynecology and Obstetrics Yozgat, Turkey
**Yozgat Bozok University Faculty of Medicine, Department of Physiology, Yozgat, Turkey*

Abstract

Aim: This study aims to evaluate the effects of alpha lipoic acid (ALA), which is a strong antioxidant, on endometriosis (EMS).

Methods: Thirty sexually-mature, female Wistar albino rats weighing 180-220 grams were separated into three groups: sham (n=10), EMS (n=10) and EMS + ALA (n=10). Blood samples were taken from the rats and were centrifuged and stored at -80 °C before forming the experimental EMS model. ALA at a dose of 50 mg/kg was orally administered to EMS + ALA group. At the end of this procedure, blood samples were taken again and were centrifuged and stored at -80 °C. Plasma total antioxidant status (TAS), plasma total oxidant status, oxidative stress (OS) index and cancer antigen 125 were studied from these samples.

Results: There were no differences between the groups in terms of baseline results. According to the second blood test results, all parameters in the sham group and all parameters other than plasma TAS in EMS + ALA group were statistically different than in EMS group ($p<0.05$). Considering the 1st and 15th day changes in the parameters of the groups, it was observed that ALA had positive effects.

Conclusion: ALA reduces OS in EMS; thus, may have a positive effect on the severity and stage of the illness and reduce recurrence after treatment.

Keywords: Endometriosis, oxidative stress, alpha lipoic acid

Öz

Amaç: Bu çalışma güçlü bir antioksidan olan alfa lipoik asitin (ALA) endometriozis (EMS) üzerine etkilerini değerlendirmeyi amaçlamaktadır.

Yöntemler: Otuz adet, 180-220 gram ağırlığında, seksüel matür, dişi Wistar albino rat üç gruba ayrılmıştır: Sham, EMS grubu ve EMS + ALA grubu. Deneysel EMS modeli oluşturulmadan ratlardan kan örnekleri alındı ve santrifüj edilerek -80 °C'de saklandı. EMS + ALA grubuna 15 gün, 50 mg/kg dozda, oral yoldan alfa lipoik asit verildi. Bu sürenin sonunda ratlarda tekrar kan örnekleri alındı ve santrifüj edilerek -80 °C'de saklandı. Bu örneklerden plazma total antioksidan status (TAS), plazma total oksidan status, oksidatif stres (OS) indeks ve kanser antijen 125 çalışıldı.

Bulgular: Grupların başlangıç sonuçları arasında farklılık yoktu. İkinci alınan kan sonuçlarında sham grubu bütün parametrelerde, EMS + ALA grubu ise plazma TAS dışındaki bütün parametrelerde EMS grubundan istatiksel olarak farklıydı ($p<0,05$). Gruplarda parameterelerin 1.-15. gün değişimine baktığımızda ALA'nın olumlu etkilerini saptadık.

Sonuç: ALA, EMS'de OS'yi azaltarak hastalığın şiddeti ve evresi üzerinde olumlu etki gösterebilir, ayrıca tedavi sonrası nüksleri azaltabilir.

Anahtar Sözcükler: Endometriozis, oksidatif stress, alfa lipoik asit

Address for Correspondence/Yazışma Adresi: Taylan Onat, Yozgat Bozok University Faculty of Medicine, Department of Gynecology and Obstetrics Yozgat, Turkey
E-mail: onat.taylan@gmail.com ORCID: orcid.org/0000-0002-8920-1444
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Introduction

Endometriosis (EMS) is a common estrogen-dependent gynecological disease defined by the presence of endometrial-like glands and stroma outside the uterine cavity. EMS is observed in 10% of women of reproductive age, and 35-50% of women with pelvic pain and/or infertility are diagnosed with EMS (1). Considering that EMS diagnosis requires histopathological verification, its frequency might be higher. It negatively affects women's health with its primary symptoms such as chronic pelvic pain, dyspareunia, dysmenorrhea and infertility. Although it mostly settles in the pelvic peritoneum, its involvement in the ovary and rectovaginal septum is considerably frequent. The risk of recurrence after treatment is quite high in the first stage of EMS (2). EMS was first defined in 1,860 but its etiopathogenesis has still not been clarified (3). The most popular theory among the various proposed theories is the theory of retrograde menstruation (Sampson) (4). However, although 90% of women have retrograde menstruation, the fact that EMS is observed to a lesser extent suggests that additional factors such as inflammatory and immune factors are effective in the development of the disease (5).

Oxidative stress (OS) is oxidant-antioxidant imbalance in favor of the oxidants. Antioxidant system consists of enzymatic (e.g. catalase, superoxide dismutase) and non-enzymatic (e.g. vitamin C and selenium) substances. Recent findings have shown that OS has a key role in the development of EMS and spread of the endometrial tissue (6,7). The idea that OS may trigger inflammation in EMS, which is a chronic inflammatory disease, is gaining currency. OS may also cause inflammation with the changes it causes in endothelial cells (increased permeability and adhesion molecule expression in endothelial cells) (6). It was found that there was a correlation between the severity of EMS and lipid peroxide activity in blood and peritoneal fluid (8). Moreover, another study determined that low GSH peroxidase and high malondialdehyde levels were found in ectopic endometrial tissue (9). In this case, it increases the possibility of using antioxidant agents in the treatment of EMS. Antioxidant agents have been used for EMS treatment in human studies and animal experiments (9-11).

Alpha lipoic acid (ALA) is a powerful antioxidant found naturally inside every cell of the human body. It has an important role in metabolism due to the fact that it is the cofactor for various mitochondrial enzymes (12). Besides its antioxidant properties, ALA helps regenerate other endogenous antioxidants such as GSH (13). Protective effect of ALA has been investigated in experimental ischemia/reperfusion (I/R) injuries (14,15). To the best of our knowledge, there has been no study examining the ameliorative effect of ALA on EMS. This study aims to examine the effects of ALA on EMS in which there are robust findings indicating that OS plays a role in its etiopathogenesis.

Methods

This study was carried out in the Saki Yenilli Production and Application Laboratory. The study was conducted in accordance with the Animals Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines after obtaining approval from the Ethics Committee of the same center (no: 01.03.01, date: 06/01/2020). Since the experimental nature of the study, informed consent was not obtained.

Thirty sexually-mature, female Wistar albino rats weighing 180-220 grams were used in this experiment. The rats were monitored for a few days before the first phase of the experiment and were determined to be healthy.

The rats were randomly dived in three groups: sham (n=10), EMS (n=10) and EMS + ALA (EMS + ALA, n=10). A combination of 7 mg/kg xylazine hydrochloride (Bayer, Turkey) and 50 mg/kg ketamine hydrochloride (Eczacıbası, Turkey) was intraperitoneally injected for anesthesia. Before starting surgical procedure, approximately 1 mL of intravenous blood was taken from all rats. These samples were centrifuged at 4,000 rpm for 10 minutes. Serums were stored at -80 °C for biochemical evaluation. The rats were put on surgical platform in the supine position. After shaving the abdominal area and cleaning with 10% povidone-iodine, approximately 2-3 cm long vertical incision was made. In the sham group, abdomen was closed with a 4/0 Vicryl Rapide Polyglactin 910 suture (Ethicon Inc., Somerville, NJ). The EMS model was formed within the frame of a procedure determined by Uygur et al. (16) in EMS and EMS + ALA groups. Skin closure was done using 4/0 Vicryl Rapide Polyglactin 910 suture. The EMS + ALA group was started ALA (Sigma-Aldrich, Darmstadt, Germany) at a dose of 50 mg/kg by oral administration using a gavage one day after the procedure, and the treatment was continued for 15 days. At the end of 15 days, second blood samples taken from the rats under anesthesia were centrifuged and stored at -80 °C.

Plasma total antioxidant status (TAS) measurement was made according to the Erel (17) method using a commercial kit (REL Assay Diagnostics, Gaziantep, Turkey). The basis of the method is the reduction of the dark blue-green ABTS radical into colorless ABTS form through antioxidant substances in the samples. 18 µL of plasma was added over 300 µL of reactive (acetate buffer 0.4 mol/L, pH=5.8) solution. The measurement was made at 660 nm wavelength after 30 seconds using a spectrophotometer device (Shimadzu UV-1800, Kyoto, Japan). Then, reactive

2 (prochromogen ABTS 30 mmol/L) solution was added and kept at 37 °C for 5 minutes and spectrophotometric measurements were made at 660 nm. For the calculation of the measurements, the absorbance change was calculated by deducting the first measurement value from the second measurement value. Then, the calculation was made according to the formula using the absorbance changes: TAS=ΔAbs H_2O - ΔAbs sample/ΔAbs H_2O - ΔAbs standard. The results were presented as mmol Trolox equivalent/L.

Plasma plasma total oxidant (TOS) measurement was made according to the Erel (18) method using the commercial kit (REL Assay Diagnostics, Gaziantep, Turkey). Oxidants in the sample oxidize the ferrous ion-chelator complex into ferric ions. Color intensity is related to the oxidant molecule amount. The measurement was made in line with the measurement protocol included in the kit. 45 µL plasma was added over 300 µL tampon solution (H_2SO_4 25 mM pH=1.75). The measurement was made at 530 nm wavelength with spectrophotometer after 30 seconds. Then, 15 µL substrate solution was added and waited for 5 minutes at 37 °C, and the measurement was repeated with the spectrophotometer device at 530 nm wavelength. For the calculation of the measurements, the absorbance change was calculated by deducting the first measurement value from the second measurement value. Calculations were made according to formula included in the kit: TOS=ΔAbs sample/ΔAbs standard x10. The results were presented as µmol H_2O_2 equivalent/L.

Oxidative stress index (OSI) was calculated using TAS and TOS results according to the following formula (19): OSI (arbitrary unit) = TOS (µmol H_2O_2 equivalent/L)/TAS (µmol Trolox equivalent/L) ×100.

Plasma cancer antigen 125 (Ca 125) level was measured by enzyme-linked immunosorbent assay using a commercial kit (Shanghai SunRed Biological Company, Catalogue no: 201-11-0448).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc; Chicago, IL, USA) version 20.0. Normality of the variables was analyzed using the Shapiro-Wilk test. Numerical data were presented as mean ± standard deviation. Intergroup differences of the numerical data were evaluated with One-Way ANOVA test. The Bonferroni test was used for the post-hoc analysis. A p value of less than 0.005 was considered statistically significant.

Results

During this procedure, in each group, one rat died. The evaluation of the blood samples taken at the beginning of the procedure (1st day) showed that there were no significant differences between the groups in terms of Ca 125, TAS, TOS and OSI values (Table 1).

Evaluation of the blood samples taken in the 15th day of the procedure showed that there was a significant difference in Ca 125, TOS and OSI values between sham and EMS + ALA groups and EMS group, and in TAS value between sham group and EMS group (Table 2).

Figure 1 and Table 3 show the comparisons of Ca 125, TAS, TOS and OSI values in the 1st and 15th days of the procedure. All parameters in EMS group showed statistically significant differences between the 1st and 15th days ($p<0.05$). There was a significant difference between Ca 125, TOS and OSI values on the 1st day and those on the 15th day in EMS + ALA group, but the difference was not as significant as in EMS group.

Discussion

This study investigates the effects of ALA treatment and the relationship between EMS and OS in an experimental rat EMS model. The study determined that ALA had positive effects on EMS through biochemical indicators. TOS, OSI and Ca 125 values were found to be significantly different in EMS + ALA group compared to EMS group.

EMS etiology is still not clear despite growing information. OS is the imbalance between free radicals such as reactive oxygen species (ROS) and antioxidant defense system. OS is thought to have a role in the

Table 1. Comparison of biochemical parameters of the groups in the 1st day

	Sham (n=10)	EMS (n=10)	EMS + ALA (n=10)	p value
Ca125	1.19±0.09	1.22±0.07	1.18±0.12	0.611
TAS	1.95±0.36	1.73±0.40	1.87±0.23	0.364
TOS	14.06±2.26	14.39±3.24	14.12±3.59	0.968
OSI	7.39±1.69	8.42±1.48	7.73±2.37	0.467

One-Way ANOVA test. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (µmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index, n: Number

Table 2. Comparison of biochemical parameters of the groups in the 15th day

	Sham	EMS	EMS + ALA	p value
Ca 125	1.25±0.16	1.62±0.15	1.32±0.16	<0.001[a,c]
TAS	1.88±0.39	1.32±0.27	1.62±0.34	0.005[a]
TOS	14.59±1.61	18.69±2.63	15.61±3.15	0.003[a,c]
OSI	8.12±2.09	13.14±2.55	9.93±2.55	<0.001[a,c]

One-Way ANOVA test. Post-hoc analysis Bonferroni test was applied. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (µmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
[a]Significantly different in sham group compared to EMS group.
[b]Significantly different in sham group compared to EMS + ALA group.
[c]Significantly different in EMS group compared to EMS + ALA group.
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index

Table 3. Comparison of the 1st and 15th day levels of the biochemical indicators of groups

Groups	Parameters	Mean	SD	p value
Sham	TAS(1)-TAS(2)	0.07	0.66	0.733
	TOS(1)-TOS(2)	-0.52	1.07	0.157
EMS	OSI(1)-OSI(2)	-0.73	3.15	0.481
	Ca 125(1)-Ca 125(2)	-0.05	0.15	0.273
	TAS(1)-TAS(2)	0.41	0.13	<0.001
	TOS(1)-TOS(2)	-4.30	2.93	0.001
	OSI(1)-OSI(2)	-4.72	2.40	<0.001
	Ca 125(1)-Ca 125(2)	-0.39	0,167	<0.001
	TAS(1)-TAS(2)	0.24	0.40	0.089
EMS+ALA	TOS(1)-TOS(2)	-1.48	1.68	0.021
	OSI(1)-OSI(2)	-2.20	2.79	0.034
	Ca 125(1)-Ca 125(2)	-0.13	0.15	0.019

Paired t test. Ca 125 (U/mL), TAS (mmol Trolox equivalent/L), TOS (μmol H_2O_2 equivalent/L) and OSI (arbitrary unit).
(1): 1st day level, (2): 15th day level
EMS: Endometriosis, ALA: Alpha lipoic acid, TAS: Total antioxidant status, TOS: Total plasma oxidant, OSI: Oxidative stress index, SD: Standard deviation

development of EMS as in numerous diseases (20-22). ROS in oviductal fluid affects the reproductive system at various levels from ovulation to implantation. Additionally, ROS molecules may cause damage by adhering to various structures in the cell. Cellular debris in oviductal fluid and erythrocytes forms a source for OS reactions. Erythrocytes are likely to release pro-oxidant and proinflammatory factors, such as heme and iron, into the peritoneal cavity. These factors play an important role in the formation of ROS if not properly cleaned from the environment (23). On the other hand, OS increases the growth and implantation of endometrial cells in the peritoneal cavity. Thus, a vicious cycle forms between EMS and OS. Jamali et al. (9) compared eutopic and ectopic endometrial cells and found that malondialdehyde (MDA) levels increased in ectopic endometrial cells while glutathione (GSH) levels decreased. Turgut et al. (22) conducted a study with 72 women who were operated for different indications and divided the patients into groups based on EMS diagnosis. While the level of OS indicators such as copper, ceruloplasmin and TAS was high in EMS group, the TAS was significantly low. Amreen et al. (8) revealed a

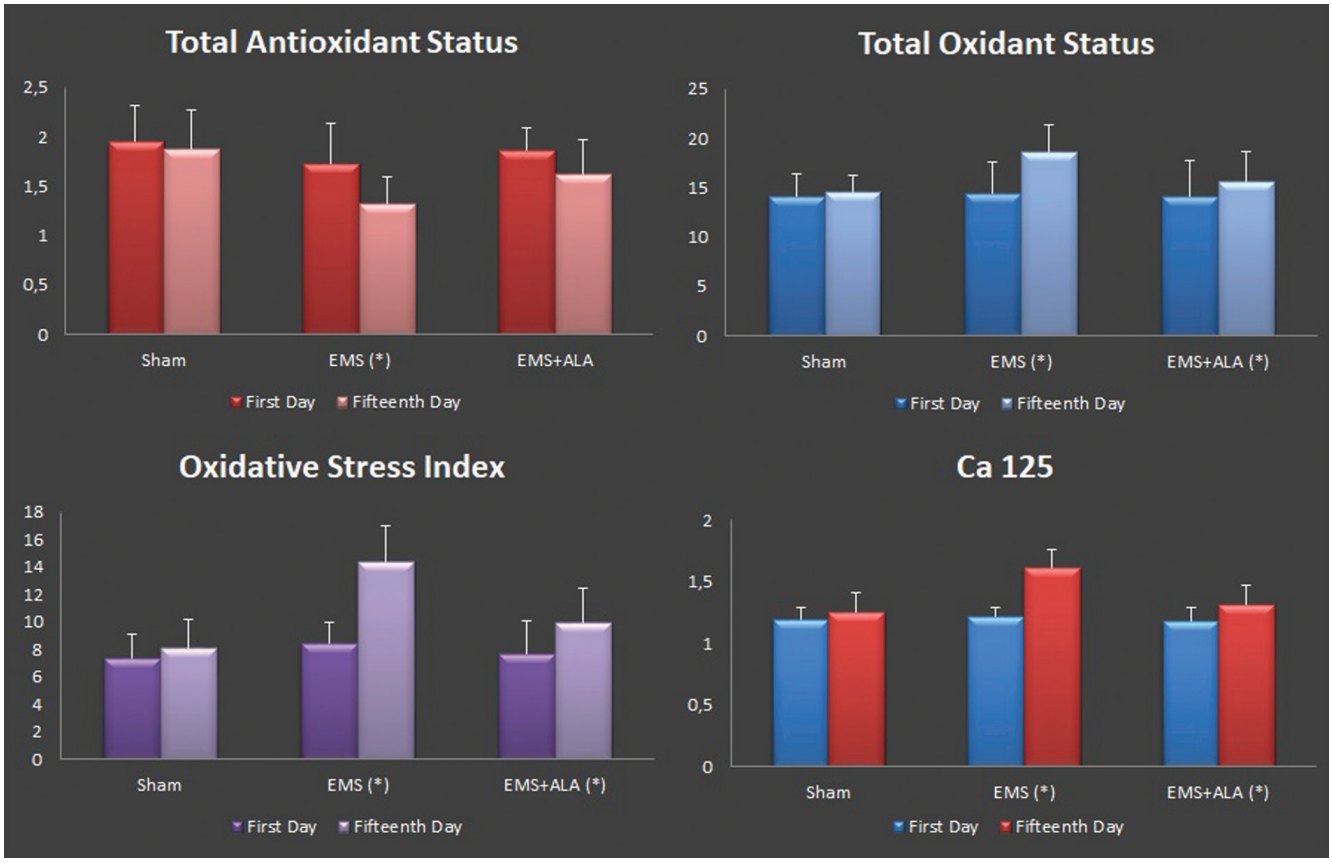

Figure 1. Comparison of the 1st and 15th day levels of the biochemical indicators of groups. [(*): The change of the biochemical indicator is statistically significant]
EMS: Endometriosis, ALA: Alpha lipoic acid

relationship between OS and disease severity. The present study found a significant correlation between EMS and OS, in line with the literature.

Ca 125, an indicator in the glycoprotein structure, is used for the evaluation of ovarian masses. However, its diagnostic value is low, similar to other cancer indicators (24). Studies showed that Ca 125 increases in various malign and benign conditions such as chronic liver diseases, EMS, pelvic inflammatory disease, ovarian, endometrium and gastrointestinal tract cancers (25-29). Studies also showed that Ca 125 level which is known to increase in EMS is correlated with the stage of illness (27). Oliveira et al. (30) revealed that Ca 125 measurement made in mid-cycle was more effective in EMS diagnosis. In the present study, we used CA 125 level to verify EMS diagnosis and found that elevated Ca 125 increased the probability of the diagnosis. Additionally, the study found that ALA treatment significantly decreased the Ca 125 level.

Cells try to be freed from oxidant stress with enzymatic and non-enzymatic antioxidant mechanisms. Numerous antioxidant substances have been used against OS in non-enzymatic chol (9-12,14). Erten et al. (11) examined the effects of vitamin C on endometriotic implants and found that vitamin C suppressed the growth of endometrial implants and reduced the size of these implants. Another study found that caffeic acid may decrease EMS-related complications by reducing OS (9). Resveratrol has been used to reduce the effects of OS and similar results obtained (31). Additionally, antioxidants have been found to be effective in reducing EMS-related pain (32). ALA is a powerful antioxidant that is a cofactor for disulfide structures and is synthesized within a number of tissues including the liver (13). 20-40% of orally taken ALA get into circulation and reach to the highest plasma concentrations within 30-120 minutes (33). A study examining the effects of ALA on intestinal I/R damage determined that there was a statistically significant difference in MDA and GSH levels between ALA-treated and nontreated rats (34). Deng et al. (35) determined that ALA in myocardial I/R had a positive effect on heart functions after I/R by reducing necrosis, apoptosis and inflammation in cardiomyocytes. As we mentioned above, there is a vicious circle between EMS and OS. We think that ALA neutralizes ROS and reduces the effects of these molecules such as inflammation, angiogenesis, adhesion and endometriotic cell differentiation. If we consider the relationship between EMS and OS, it can be said that ALA had a positive effect on EMS in our study.

Study Limitations

The limitations of this study were that EMS was evaluated with only biochemical methods, and histopathological verification was not done. Another limitation is that the verification rate of the study results in humans is low due to the fact that it was an animal study.

Conclusion

EMS is a chronic disease that tends to relapse despite various treatments. ALA with proven antioxidant effect reduces OS in EMS; thus, may positively affect the severity and stage of illness and reduce recurrence after treatment. In order to confirm our results, studies including histopathological evaluation are needed.

Authorship Contributions

Concept: T.O., M.Ç., Design: T.O., M.Ç., Data Collection or Processing: T.O., M.Ç., Analysis or Interpretation: T.O., M.Ç., Literature Search: T.O., M.Ç., Writing: T.O., M.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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