The Egyptian Cardiothoracic Surgeon

Vol. 2, No. 3, 77 - 83

Original Article

Effect of Alpha-Lipoic Acid on Atrial Fibrillation after Open Heart Surgery

Wael Elfeky[1], Dalia R El-Afify[2]

[1] Department of Cardiothoracic Surgery, KafrElsheikh faculty of medicine, KafrElsheikh, Egypt

[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Tanta University, Egypt

Abstract

Background: Postoperative atrial fibrillation (POAF) is associated with increased morbidity and mortality, and an inflammatory process is involved in its pathogenesis. We aimed to study the possible effect of alpha-lipoic acid (ALA) as an antioxidant on atrial fibrillation after cardiac surgery.

Methods: The study included ninety patients who underwent cardiac surgery, either valvular or coronary artery bypass grafting using cardiopulmonary bypass, and were randomized into two groups: Control and ALA groups. Blood samples were obtained to measure preoperative and postoperative levels of malondialdehyde (MDA), glutathione, C-reactive protein (CRP) and interleukin-6 (IL-6). The patients were monitored for the occurrence of atrial fibrillation until the day of discharge.

Results: POAF occurred in 33% in the control group versus 11% in the ALA group (p=0.011). When compared to the control group, ALA significantly decreased the postoperative levels of MDA (4.78±0.91 vs. 5.36±1.03 nmol/ml; p= 0.006) CRP (19.44±3.14 vs. 26.56±6.29 mg/dl; p <0.001) and IL-6 (22.25±2.2 vs. 25.37±2.5 pg/ml; p< 0.001) while glutathione level increased significantly in patients who received ALA (26.4±4.59 vs. 23.44±5.11 mg/l; p= 0.005).

Conclusion: ALA may help in the prevention of atrial fibrillation following cardiac surgery through exerting antioxidant and anti-inflammatory effects.

KEYWORDS

POAF; Alpha-lipoic acid; Oxidative stress; Glutathione; Interleukin 6

Article History

Submitted: 24 Jan 2020

Revised: 12 Feb 2020

Accepted: 20 Feb 2020

Published: 1 July 2020

Introduction

Postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery, which is associated with a longer hospital stay, and it may lead to the development of stroke, heart failure, and thromboembolic events [1]. The pathophysiology POAF is complex and involves several factors, including ischemia, inflammation, oxidative stress, sympathetic activation, and atrial distension [1,2]. Cardiopulmonary bypass (CPB) and ischemic reperfusion injury are associated with an inflammatory process and oxidative stress that may lead to cardiac tissue remodeling, cardiac function impairment, and development of POAF [3,4]. Several studies have shown that some antioxidants such as vitamin C, vitamin E, polyunsaturated fatty acids (PUFAs) and N-acetyl cysteine could reduce the incidence of POAF and can be used for prevention [5-9]. Alpha-lipoic acid (ALA) is an antioxidant that has many properties including the decrease of reactive oxygen species, regeneration of endogenous antioxidants such as vitamin C and glutathione, prevention of lipid and protein peroxidation and decreasing oxidative stress [10,11] and it was reported that ALA could prevent cardiac dysfunction in some animal studies [12-14]. Glutathione is an endogenous intracellular antioxidant, while malondialdehyde

Corresponding author: Wael Elfeky waelfeky@yahoo.com

Table 1: The clinical pre-operative and operative data of both control and ALA groups. Continuous data are presented as mean and standard deviation and categorical data as number and percent.

Parameter		Control group (n= 45)	ALA group (n= 45)	p-value
Age (years)		43.07±13.53	41.13±14.16	0.549
Gender M/F		26/19	27/18	0.849
Hypertension		14 (31%)	13 (29%)	0.818
Diabetes Mellitus		10 (22%)	11 (24%)	0.803
Heart rate (beat/min)		77±12	76±12	0.688
Ejection fraction %		61.2±9.7	62.4±8.5	0.528
Left atrial diameter (mm)		44.4±6.4	43±7.6	0.349
Surgery	CABG	17 (38%)	18 (40%)	0.829
	Valvular surgery	28 (62%)	27 (60%)	
Aortic clamp time (min)		69.5±25.69	70.89±23.46	0.801
CPB time (min)		90.4±37.05	92.56±33.65	0.773
Preoperative MDA (nmol/ml)		3.89±0.82	3.98±0.79	0.576
Preoperative glutathione (mg/dl)		30.15±6.2	30.8±5.5	0.602
Preoperative CRP (mg/L)		6.75±2	7.92±1.4	0.641
Preoperative IL-6 (pg/ml)		18.6±2	18.54±1.45	0.873

ALA: Alpha-lipoic acid; MDA: malondialdehyde; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; CRP:C-reactive protein, IL-6: interleukin-6

(MDA) results from polyunsaturated fatty acid peroxidation, and measurement of glutathione and MDA can reflect the oxidative stress status. On the other hand, C-reactive protein (CRP) and interleukin-6 (IL-6) are inflammatory markers that may affect the development of POAF [4].

The effect of ALA on postoperative AF has not well-established clinically. Therefore, the objectives of our study were to investigate the impact of ALA as an antioxidant on oxidative stress and the inflammatory process in patients undergoing on-pump cardiac surgery and its effect on POAF.

Patients and Methods:

This randomized controlled clinical study was performed in the Cardiothoracic Surgery Department in our university hospital after the approval of the research ethics committee, and the patients' consent was obtained before randomization. We included patients with normal sinus rhythm undergoing primary cardiac valve surgery or coronary artery bypass grafting (CABG). We excluded patients with a history of atrial fibrillation (AF), congenital heart disease, conditions that alter oxidative stress status, and induce inflammation such as cancer and recent infection, administration of corticosteroid, or non-steroidal anti-inflammatory drugs, off-pump technique and emergency or redo surgery. No posterior pericardiotomies were carried out in any of the patients in both groups.

Our study included ninety patients who were randomized into two groups: the control group (n= 45) who received the placebo and the ALA group (n= 45) who received alpha-lipoic acid. ALA was given in a dose of 600mg twice daily starting 5-10 days before surgery and continued when oral intake is allowed after surgery till the day of discharge.

Venous blood samples were obtained preoperatively (before administration of placebo or ALA) and postoperatively (48 hours after surgery) to measure the following biochemical parameters: blood glutathione level which was measured according to Chavan and colleagues method [15]; serum malondialdehyde (MDA) was determined as thiobarbituric acid reactive substances (TBARS) depending on the method of Draper and Hadley [16]; Interleukin-6 (IL-6) was measured using Elisa kit (Raybiotech Inc, USA), and C-reactive protein (CRP) levels which were determined by quantitative turbidimetric method

Table 2: The changes in oxidative stress and inflammatory markers before and after surgery. Continuous data are presented as mean and standard deviation.

Parameter	Control group (n=45)			ALA group (n=45)		
	Preoperative	Postoperative	P	Preoperative	Postoperative	P
MDA (nmol/ml)	3.89±0.82	5.36±1.03	<0.001	3.98±0.79	4.78±0.91	<0.001
Glutathione (mg/L)	30.15±6.2	23.44±5.11	<0.001	30.8±5.5	26.4±4.59	<0.001
CRP (mg/L)	6.75±2	26.56±6.29	<0.001	7.92±1.4	19.44±3.1	<0.001
IL-6 (pg/ml)	18.6±2	25.37±2.5	<0.001	18.54±1.4	22.25±2.2	<0.001

ALA: Alpha lipoic acid, MDA: malondialdhyde, CRP:C-reactive protein, IL-6: interleukin-6.

using commercial kits (Spinreact, Ctra Santa Colona, Spain).

Statistical Analysis

SPSS version 15 (IBM Corp- Chicago- IL, USA) was used for data analysis. The Chi-square test (X2) was used for the comparison of qualitative data. The t-test was to compare the means of quantitative data of the two groups and paired t-test for comparison of data within the same group before and after surgery. Kaplan-Meier survival curve was used to determine the cumulative incidence of POAF in each group, and the survival curves of the two groups were compared using the log-rank test. A p-value of less than 0.05 was considered statistically significant.

Results

The study included ninety patients with a mean age of 42± 14 years; 45 patients underwent valvular surgery, and 45 patients underwent CABG. Table 1 shows the clinical preoperative and operative data of both control and ALA groups.

There was no significant difference regarding age, gender, history of hypertension, and diabetes mellitus between the two studied groups. The preoperative data, including heart rate, ejection fraction, and left atrial diameter, were not significantly different between control and ALA groups. The operative data were not significantly different regarding the type of surgery, aortic clamp, and CPB time, as shown in Table 1.

Concerning oxidative stress markers, both control and ALA groups had no significant difference in preoperative MDA and glutathione levels. The preoperative levels of the inflammatory markers CRP and IL-6 were not significantly different between the two studied groups, as presented in (Table 1).

The postoperative levels of MDA, CRP, and IL-6 significantly increased, and the postoperative glutathione significantly decreased in both control and ALA groups compared to their baseline preoperative data (p<0.001) as presented in (Table 2). However, the ALA group had significantly lower levels of postoperative MDA, CRP, and IL-6 and significantly higher levels of postoperative glutathione compared to their respective values in the control group, as shown in Table 3.

The incidence of POAF was significantly decreased in the ALA group (11%) compared to in control group (33%) (Log-rank test p=0.01), as shown in the Kaplan-Meier survival curve for the occurrence of POAF in both control and ALA groups Figure 1.

Table 3: Effect of ALA on MDA, glutathione, CRP, and IL-6 levels. Data are presented as mean and standard deviation.

Parameter	Control group (n= 45)	ALA group (n= 45)	p-value
Postoperative MDA (nmol/ml)	5.36±1.03	4.78±0.91	0.006
Postoperative Glutathione (mg/L)	23.44±5.11	26.4±4.59	0.005
Postoperative CRP (mg/L)	26.56±6.29	19.44±3.14	<0.001
Postoperative IL-6 (pg/ml)	25.37±2.5	22.25±2.2	<0.001

ALA: Alpha lipoic acid, MDA: malondialdhyde, CRP:C-reactive protein, IL-6: interleukin-6

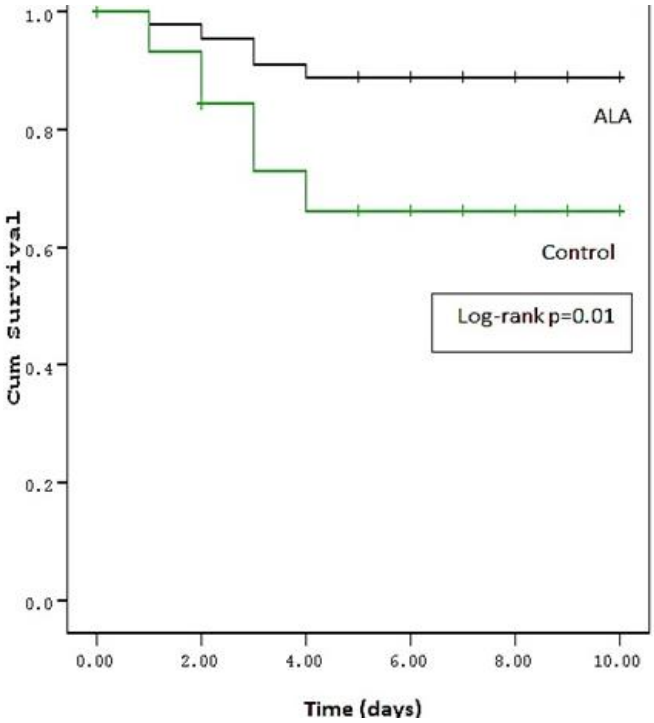

Figure 1: Kaplan-Meier curve for the occurrence of post-operative atrial fibrillation in control and alpha lipoic acid groups (Log-rank p=0.01).

Discussion

Atrial fibrillation after cardiac surgery was linked to several predisposing factors, including old age, history of hypertension, diabetes, and left atrium diameter, cardiopulmonary bypass, and aortic clamp times [1,2]. Both control and ALA groups had no significant difference regarding all the previous factors. In this study, ALA significantly decreased the incidence of POAF compared to the control group, and it is consistent with other clinical studies which reported that perioperative supplementation of other several antioxidants including vitamin C, vitamin E, polyunsaturated fatty acids and N-acetyl cysteine reduced the incidence of atrial fibrillation after cardiac surgery [5-9]. Additionally, ALA significantly decreased the inflammatory markers, and the oxidative stress marker, and significantly increased the endogenous glutathione levels.

Inflammatory reaction and oxidative stress play an essential role in the pathogenesis of POAF, and increased levels of inflammatory cytokines and oxidative stress were recorded in patients who had atrial fibrillation after cardiac surgery compared to other patients who did not have POAF [1,2].

Surgical trauma, cardiopulmonary bypass, and ischemic reperfusion injury are the main triggering factors for tissue damage and the increase in the production of inflammatory mediators [3,4]. This explains the significant increase in postoperative levels of CRP and IL-6 in both control and ALA groups.

High levels of inflammatory markers, including CRP, tumor necrosis factor-α (TNF-α), IL-6, and IL-1β, were associated with the development of POAF [4,17,18]. The release of inflammatory cytokines increases neutrophil migration and activation that leads to impairment of atrial conduction and diminishes the refractory period of cardiomyocytes leading to the development of atrial fibrillation [19]. The increase in the level of IL-6 during cardiac surgery starts after 10 minutes after the reperfusion and continues to increase [20]. IL-6 can negatively affect the cardiac function as it induces impairment in the myocardial contractile function, alters the response of cardiac β-adrenergic receptors, and induces left ventricular remodeling [21,22].

In our study, ALA significantly reduced the level of postoperative CRP and IL-6 compared to the control group, and this result is in agreement with Sardu and colleagues who reported that ALA administration significantly reduced the circulating levels of inflammatory markers in patients with atrial fibrillation after one year of catheter ablation [23]. This decrease in the level of inflammatory markers may be explained by ALA's ability to suppress the activation of redox-sensitive transcription factor nuclear factor-κB (NF-κB) that regulates the expression of inflammatory cytokines [24].

Cardiopulmonary bypass and ischemic reperfusion injury are also associated with an increase in the production of reactive oxygen species and the development of oxidative stress [25]. This explains the significant increase in postoperative oxidative stress markers MDA and a considerable decrease in postoperative endogenous antioxidant glutathione in both control and ALA groups. The increased oxidative stress was reported to be associated with the

development of POAF [26]. Oxidative stress can lead to atrial cellular changes with disruption of electrical activity, shortening of the effective refractory period, and atrial remodeling that contribute to the development of POAF [27]. In addition, increased levels of reactive oxygen species increase the activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) pathway, which results in increasing the inflammatory response and modulation apoptosis [28].

In the present study, ALA significantly decreased postoperative MDA levels and significantly increased postoperative glutathione levels compared to the control group, which is consistent with pre-clinical studies that reported that ALA could reduce MDA levels and decrease ischemic reperfusion injury [29].

The increase in postoperative glutathione levels can be explained by the ability of ALA to recycle endogenous antioxidants [11] and increasing the synthesis of glutathione through enhancing cellular cysteine uptake that is necessary for glutathione synthesis [30]. On the other hand, the decrease of postoperative MDA levels can be explained by the antioxidant properties of ALA and increased endogenous glutathione levels.

Our findings suggest that ALA antioxidants may reduce the occurrence of atrial fibrillation after open heart surgery as it reduced oxidative stress and inflammatory cytokines such as IL-6.

Study limitations

The study included small sample size, and the study period was short. It is recommended to perform other studies on a larger number of patients and for a longer period of follow up. It is preferred to study the effect of ALA on patients undergoing a single type of cardiac surgery, either CABG or valvular surgery. This is a single-center study, and generalization of the results may be an issue.

Conclusion

Alpha-lipoic acid may help in the prevention of atrial fibrillation following open-heart surgery through exerting antioxidant and anti-inflammatory effects.

Conflict of interest: Authors declare no conflict of interest.

References

1. El-Chami MF, Kilgo P, Thourani V, et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol 2010; 55:1370–1376.
2. Anatol´evna RO, Veniaminovich FO, Mikhaylovich KS. Predictors of new-onset atrial fibrillation in elderly patients with coronary artery disease after coronary artery bypass graft. Journal of Geriatric Cardiology 2016;13: 444-449
3. Koroglu S, Tuncer C, Acar G, et al. Relation of inflammatory and oxidative markers to the occurrence and recurrence of persistent atrial fibrillation. Turk Kardiyol Dern Ars. 2012; 40: 499–504.
4. Elahi MM, Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concept of oxidative stress-mediated myocardial injury phenomenon. Eur J Cardiovasc Prev Rehabil 2008; 15: 735–41.
5. Rodrigo R, Korantzopoulos P, Cereceda M, et al. A randomized controlled trial to prevent post-operative atrial fibrillation by antioxidant reinforcement. J Am Coll Cardiol. 2013;62 (16): 1457-1465.
6. Liu, XH, Xu CY and Fan GH. Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials. BMC Cardiovascular Disorders 2014, 14: 52-60
7. Ali-Hassan-Sayegha S, Mirhosseini SA, Rezaeisadrabadia M, et al. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interactive CardioVascular and Thoracic Surgery 2014; 18: 646–654.
8. Shi R, Li ZH, Chen D, Wu QC, Zhou XL, Tie HT. Sole and combined vitamin C supplementation can prevent postoperative atrial fibrillation after cardiac surgery: A systematic review and

meta-analysis of randomized controlled trials. Clin Cardiol. 2018;41(6):871-878.
9. Costanzo S, di Niro V, Di Castelnuovo A, et al. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. Thorac Cardiovasc Surg. 2013; 146 (4): 906-11.
10. Park S, Karunakaran U, Jeoung NH, Jeon JH, Lee IK. Physiological effect and therapeutic application of alpha lipoic acid. Curr Med Chem. 2014; 21 (32): 3636-45.
11. Jones W, Li X, Qu ZC, Perriott L, Whitesell RR, May JM. Uptake, recycling, and antioxidant actions of alpha-lipoic acid in endothelial cells. Free Radic Biol Med 2002; 33: 83-93.
12. Deng C, Sun Z, Tong G, et al. α-Lipoic acid reduces infarct size and preserves cardiac function in rat myocardial ischemia/reperfusion injury through activation of PI3K/Akt/ Nrf2 pathway. PLoS ONE. 2013; 8 (3), e58371
13. Dudek M, Knutelska J, Bednarski M, et al. Alpha lipoic acid protects the heart against myocardial post ischemia-reperfusion arrhythmias via KATP channel activation in isolated rat hearts. Pharmacol Rep. 2014; 66 (3): 499-504
14. Kurumazuka D, Kitada K, Tanaka R, et al. α-Lipoic acid exerts a primary prevention for the cardiac dysfunction in aortocaval fistula-created rat hearts. Heliyon. 2019; 5, e02371
15. Draper H, Hadly M. Malonaldehyde determination as an index of lipid peroxidation. Methods Enzymol 1990; 186: 421-431.
16. Chavan S, Sava L, Saxena V, Pillai S, Sontakke A, Ingole D. Reduced glutathione: importance of specimen collection. Indian J Clin Biochem 2005. 20:150-152.
17. Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. Int J Cardiol. 2013; 169: 62–72.
18. Ucar HI, Tok M, Atalar E, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. Heart Surg Forum 2007; 10: E131–E135.
19. Ishii Y, Schuessler RB, Gaynor SL, et al. Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. Circulation. 2005; 111: 2881–8.
20. Zahler S, Massoudy P, Hartl H, Hahnel C, Meisner H, Becker BF. Acute cardiac inflammatory responses to postischemic reperfusion during cardiopulmonary bypass. Cardiovasc Res. 1999; 41: 722–730.
21. Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. J Clin Invest. 1993; 92: 2303–2312.
22. Gulick T, Chung MK, Pieper SJ, Lange LG, Schreiner GF. Interleukin 1 and tumor necrosis factor inhibit cardiac myocyte beta-adrenergic responsiveness. Proc Natl Acad Sci U S A. 1989; 86, 6753–6757.
23. Sardu C, Santulli G, Santamaria M, et al. Effects of α-Lipoic Acid on Multiple Cytokines and Biomarkers and Recurrence of Atrial Fibrillation within One Year of Catheter. Ablation Am J Cardiol. 2017; 119(9): 1382–1386.
24. Hofmann MA, Schiekofer S, Isermann B, et al. Peripheral blood mononuclear cells isolated from patients with diabetic nephropathy showed increased activation of the oxidative-stress sensitive transcription factor NF-kB. Diabetologia 1999; 42:222-232
25. Venardos KM, Perkins A, Headrick J, Kaye DM. Myocardial ischemia-reperfusion injury, antioxidant enzyme systems, and selenium: a review. Curr Med Chem. 2007; 14: 1539–1549.
26. Oktay V, Baydar O, Sinan UY, et al. The effect of oxidative stress-related with ischemia-reperfusion damage on the pathogenesis of atrial fibrillation developing after coronary artery bypass graft surgery. Arch Turk Soc Cardiol. 2014;42(5):419-425
27. Wagoner DRV. Electrophysiological remodeling in human atrial fibrillation. Pacing and Clinical Electrophysiology, 2003; 26 (7): 1572–1575.
28. Grossini E, Molinari C, Caimmi PP, Uberti F, Vacca G. Levosimendan induces NO production through p38 MAPK, ERK and Akt in porcine coronary endothelial cells: role for mitochondrial K(ATP) channel. Br J Pharmacol. 2009; 156, 250–261.
29. He L, Liu B, Dai Z, et al. Alpha lipoic acid protects heart against myocardial ischemia-reperfusion injury through a mechanism involving aldehyde

dehydrogenase 2 activation. Eur J Pharmacol. 2012; 678(1-3): 32-8.
30. Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential. Biochim Biophys Acta 2009; 1790 (10): 1149-1160.