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Biochemical effect of alpha –lipoic acid on oxidative stress and dysfunction in experimentally induced myocardial infarction

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Abstract

The present study was designed to evaluate the protective effect and treatment effect of Alpha lipoic acid administration on cardiac necrosis markers, some electrolytes and cardiac tissue antioxidants in myocardial necrosis induced experimentally in rats- The investigated serum and cardiac biochemical parameters were: A) Serum levels of creatine kinase (CK) ,creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), total protein (T.P), albumin (Alb), glucose, calcium (Ca), sodium (Na), potassium (K), phosphorus (P). B) RBCs glucose 6 phosphate dehydrogenase (G-6-PDH). C) Cardiac antioxidants (SOD and CAT) and cardiac oxidant (MDA).

Key Words: Alpha – Lipoic Acid, Oxidative Stress, Myocardial Infarction and calcium.

Introduction

Myocardial infarction is a sudden deprivation of circulating blood may result from prolonged vasos-pasm, inadequate myocardial blood flow (eg, hypo-tension) excessive embolic occlusion vacuities, aortic root or coronary artery dissection, or aortitis (Eman, 2014).

Myocardial infarction is the major killer in the western industrialized countries. It is an ischemic necrosis of apart of cardiac muscle as a result of persistent cessation of its blood supply. It occurs when myocardial ischemia exceeds a critical thre-shold and overwhelms myocardial cellular repair mechanisms that are designed to maintain normal operating function and homeostasis. Isc-hemia at this critical threshold level for an ext-ended time period results in irreversible myocardial cell damage or death (Jensen et al., 2001).

Clinical presentation of patients is a key component in overall evaluation of the patients with myoca-rdial infarction (MI), in addition to electrocardio-gram (ECG) abnormalities and the appearance of cardiac markers in the circulation. Cardiac markers help to diagnosis MI. These biomarkers of myo-cardial necrosis include cardiac troponin I and T (cTnI and cTnT), creatine kinase (CK), myoglobin, lactate dehydrogenase, and creat-ine kinase MB (CK-MB) by mass assay is an acc-eptable alternative when cardiac troponin is not available. The other biomarkers have low spec-ificity for cardiac injury and specific alternative biomarkers of necrosis are available (Wu et al., 2004).

Acute myocardial infarction (AMI) is the most common cause of death in the world. World Health Organization (WHO) estimated the incidence of AMI with about 1.5 million occurring per year and 12.6% of death of AMI's worldwide and incidence of AMI increase with age and tends to be male pre-dominance, pre-menopausal women appear to be protected up to approximately 70 years, when the sexes converge to equal incidence. Elderly people tend to have higher rates morbidity and mortality from their infarcts (Liew et al., 2006)

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The laboratory diagnosis of MI depends on the detection of serum enzymes that are released from the irreversibly injured myocardial cells into the circulation. These enzymes are creatin kinase and lactate dehydrogenase. Many options are available for the treatment of MI. These include the use of pharmacological agents to dissolve occlusive thrombi and to prevent or delay necrosis of myocardium and mechanical procedures to recanalize occluded coronary arteries (Wenger et al., 2002)

Cardiovascular diseases (CVDs) such as hypertension and myocardial infarction (MI) are the most important cause of mortality in developing countries due to changing life styles (Rajadurai and prince, 2007).

Ischemia caused due to reduced blood supply to heart causes several biochemical alterations which may lead to cardiac dysfunction ultimately cell death. It is well recognized that free radicals generated in ishemic tissues causes metabolic stresses which results in degradation of tissue defense system, leading to myocardial damage and necrosis (Ojha et al,2011).

Experimental and clinical studies on heart failure have shown that there is increased generation of reactive oxygen species such as super oxide anion (O) and hydroxyl radical (OH) which are involved in the formation of lipid peroxide, cell membrane damage, and destruction of antioxidative defense system (Upaganlawar and Balaraman 2011).

Modern drugs are effective in preventing the cardiovascular disorders, their use often limited because of their side effects and adverse reactions (Thippeswamy et al., 2009).

α- lipoic acid has potent antioxidant activity and is clinically used to treat diabetic neuropathy. Moreover, alpha lipoic acid enhance insulin-stimulated glucose disposal; to improve peripheral microcirculation and reduce neuropathic symptoms, possibly through attenuated oxidative stress (Vessal et al., 2003).

α-Lipoic acid is a naturally occurring free radical scavenger and transition metal chelator. α-Lipoic acid is also a cofactor for mitochondrial pvruvate dehydrogenise and has been termed "metabolic antioxidant" (Packer et al., 1997).

α-LA is a vital cofactor in the multienzyme complexes that catalyze the oxidative decarboxylation of α-keto acids. It plays an important role in lipid biosynthesis by replacing coenzyme. In addition to its cofactor role, α-LA is a powerful antioxidant and possesses numerous cellular functions as well as beneficial effects in conditions with elevated oxidative stress (Arivazhagan et al., 2002).

2-Materials and Methods

Experimental design:

A total number of 120 male albino rats of (12-16 weeks) old. The body weights of them were measured on the first day of the experiment then divided into 4 groups, 30 rats each, placed in individual cages and classified as follow:

Group I: (Control group) consist of 30 rats fed ordinary rat ration.

Group II: (Heart necrosis group) (ISO group) composed of 30 rate fed ordinary rat ration and injected subcutaneously with ISO protenol at a dose of (5mg/kg, B.W in 1ml saline) weekly for 8 weeks.

Group III:(Treated group) (ISO + ALA group) consist of 30 rats fed ordinary rat ration and injected subcutaneously with ISO protenol at a dose of (5-mg/kg, B.W in 1ml saline) and intrapertonally by alpha lipoic acid at a dose of (54mg/kg B.W) weekly for 8 weeks.

Group IV: (Protected group) (ALA + ISO+ ALA) composed of 30 rate injected intra per toneal with ALA at adose of (54mg/kg, B.W) weekly for 2 month then injected with ISO at a dose of (5mg/kg B.W S/C) and ALA at a dose of (54mg/kg B.W I/P) weekly for 8 weeks.

Blood samples are collected 3 times after the 3rd injection, 6th injection and one week after the 8th injection.

Blood samples were divided in to 2 parts:

First : Serum samples separated by centrifugation at 3000 r.p.m. for 15 minutes. the clear serum was received in dry sterile tubes and used directly for determination of the following biochemical parameters:

1) Creatine kinas (CK).
2) Creatine kinase MB (CK-MB).
3) Lactate dehydrogenase (LDH).
4) Aspartet amino transferase (AST).
5) Total protein (T.P).
6) Albumin (Alb).
7) Glucose.
8) Calcium (Ca).
9) Sodium (Na).
10) Potassium (K).
11) Phosphorus (P).

Second: Heparinized tubes were collected for the determination of Glucose 6 phosphate dehydrogenase

Tissue samples: Ten rats were sacrificed at 3rd, 6th injection and one week after the 8th injection and tissue samples were collected from control and protective groups (control, ISO, treatment and protective) for determination of antioxidant enzymes; catalase (CAT) and superoxide dismutase (SOD), L- malondialdehyde (L-MDA).

From obtained results, it could be concluded that, ISO induced myocardial infarction in male rats resulted in significant increase in creatine kinase, creatine kinase MB, LDH, AST, glucose, calcium and sodium in serum, in addition to significant increase in glucose -6-phosphate dehydrogenase in RBCs. Also, it resulted in significant decrease potassium and phosphorus in serum. Furthermore, this study demonstrated that, there was significant

decrease in heart SOD and CAT activities as well as, significant increase in heart MDA levels, in ISO injected rat.

The findings of the present study demonstrated that ALA administration is effective against myocardial infarction and oxidative damage in heart tissue induced by ISO in rats. Since, ALA was able to ameliorate serum biochemical parameters, enzymatic antioxidant defense system and to prevent the lipid peroxidation in heart tissue. These results may contribute to better understanding of the heart treatment and protective roles of ALA, emphasizing the influence of it in the diet for human health, for preventing cardiovascular complications. So we recommended that, administration of diet rich in ALA is very important for protection of different body organs, especially heart against oxidative stress. Also, we strongly support that, the use of ALA as pure active ingredient in pharmacological industry for production of new drugs used as therapeutics for treatment and protection from heart diseases.

Also, ALA has cardioprotective role in isoproterenol induced myocardial infarction in rats.

5. DISCUSSION

Myocardial infarction, commonly known as heart attack is a disease occurs when the blood supply to a part of the heart is interrupted, causing death of heart tissue. It means necrosis of a region of myocardium, caused by an interruption in the supply of blood to the heart usually as aresult of occlusion of a coronary artery (Upaganlawar et al., 2011).

Isoproterenol also produces excessive free radicals resulting from oxidative metabolism of catecholamine. There are increasing evidences that cardiotoxicity of ISO occurs through oxidative mechanism (Remiao et al., 2001). Animals were treated with ALA, found to have good prophylactic effect (Ithayarasi and Devi, 1997).

1) Cardiac marker enzymes (CK, CK-MB, LDH and AST):

The data presented in tables 4 and figures 4 recorded significant increase in the activity of serum AST activity in protection group after ALA administration to normal rat indicating that the supplement has no toxic effects on the liver (De Marco et al, 2005).

Results of this study are in harmony with (Dicter et al, 2002) who showed that serum AST activity significantly increase in the group fed on any source of ALA .

Administration of ALA before and after isoproterenol injection (protective and treated group) in tables (1, 2, and 3) and figures (1, 2, and 3) showed significant decrease in serum CK, CK-MB, LDH and AST activities when compared to ISO group and that may be due to the fact that, ALA is sulpher containing vitamin and its related organ sulfur compounds have potent antioxidant activity, detoxifying and other properties (Fayed 2014).

2) Serum glucose:

The hypoglycemic effect of ALA may be due to stimulating glycogenesis or enhancing glucose utilization by inhibition of glucose absorption from the intestine (Cremer et al, 2006)

Furthermore, in isoproterenol induced myocardial infracted rats, blood glucose level was found to be increased, whereas heart tissue glycogen level was found to be decreased when compared to control animals (Rajendranand Basha, 2008).

Administration of ALA before and after isoproterenol injection (protective and treated group showed in table (5) and figure (5) showed significant decrease in serum glucose and that may be due to the antioxidative property of sulpher containing of ALA which cannormalize the oxidative stress produced by ISO (Fayed 2014).

3) Erythrocytes G6PDH:

Data represented in Table (6) and Figure (6) showed significant decrease in G6PDH in protective group after ALA administration to normal rat and that may be because ALA depressed the activities of lipogenic and cholesterogenic enzymes such as Malic enzyme, fatty acid synthase, glucose 6 phosphate dehydrogenase and 3-hydroxy-3-methyl-glutryl CoAreductase (Marwa 2014).

Administration of ALA before and after isoproterenol injection (protective and treated groups) in table (6) and figure (6) showed significant decrease in G6PDH may be due to the ability of ALA to inhibit lipid peroxidation lipid synthesis and cholesterol synthesis (Pack et al, 2002)

4) Serum calcium, sodium, potassium and phosphorus:

Data represented in table (7, 8, 9 and 10) and figure (7, 8, 9 and 10) showed significant increase in serum K and P and significant decrease in serum Ca and Na in protective group after ALA administration to normal rat.

These results are in agreement with (Goraca et al, 2011) who stated that ALA significantly reduced serum sodium and that probably resulted from a decrease in renal reabsorption of sodium with consequent excretion of sodium in urine. Increased excretion of sodium is usually associated with excess water loss as uremia.

Administration of ALA before and after isoproterenol injection (protective and treated groups) in tables (7, 8, 9 and 10) and figures (7, 8, 9 and 10) showed significant decrease in serum Ca, Na with significant increase in serum K, P.The results are in agreement with (Chatty et al, 2004) who concluded that ALA might have a significant role on cardiovascular functions. The addition effect of dietary ALA on the mineral bioavailability have been tested because of their antioxidant effect that protect some important minerals against the oxidative damage and also prevent the oxidation of

some important fatty acids that enhance mineral bioavailability (Marwa 2014)

5) Heart tissue superoxide dismutase and Catalase

Data represented in table (11 and 11) and figure (11 and 11) showed significant increase in tissue SOD, CAT activities in protective group after ALA administration to normal rats and that may be due to the antioxidant activity of ALA to scavenge reactive oxygen species and to enhance the cellular antioxidant enzymes SOD and CAT in cells (Shay et al, 2009).

The obtained data in tables (11 and 12) and figures (11 and 12) recorded significant decrease in tissue SOD and CAT in ISO group when compared to control rats and that may be due to Isoproterenol produce quinones which react with oxygen to generate superoxide anions (O_2.-) and H_2O_2, which have damaging effects in cells (Rathore et al, 2000).

Decrease in the values of SOD and CAT following isoproterenol administration indicate overwhelming of free radicals, which ensures oxidative damage to the myocardium (Ojha et al, 2013).

Administration of ALA pre and post ISO injection in protective and treated groups in tables (11 and 12) and figures (211 and 12) showed significant increase in tissue SOD and CAT when compared to ISO group and that may be due to ALA increased the activity of SOD and CAT and it scavenges superoxide radicals so reduces the myocardial damage caused by free radicals (Saravanan and Prakash, 2004).

6) Heart tissue L-Malondialdhyde (MDA):

Data represented in table (13) and figure (13) showed anon significant increase in tissue MDA (one of the end products of lipid peroxidation processes) after ALA administration to normal rats in protective group. The results are in agreement with Heinisch et al (2010) who reported that ALA has antioxidant properties, could have inhibited lipoxygenase enzymes, increase the antioxidant capacity

Lipid peroxides, decreased significantly in tissue after ALA treatment, Treatment of rats with the antioxidant ALA controlled lipid peroxidation (Dicter et al, 2002)

Data represented in table (13) and figure (13) showed significant increase in tissue MDA in ISO group when compared to control this may be due to excessive formation of free radicals by auto-oxidation of ISO and activation of the lipid peroxidative process, resulting in irreversible damage to the heart in animals subjected to ISO stress (Shaik et al, 2012).

Administration of ALA pre and post ISO injection (protective and treated groups) in Table (13) and Figure (13) showed significant decrease in tissue MDA when compared to ISO group and that may be due to increased the antioxidant potential and antioxidant enzyme activities (SOD) as a protective mechanism against oxidative stress (Arivazhaganet al., 2000).

7) Protein

In this study, decreased levels of serum total proteins were observed in isoproternol induced rats .Adecrease in serum total proteins could be due to increased free radicals production by the adminstration of isoproternol (Saranya et al, 2012).

A decrease in the levels of total proteins and A/G ratio could be due to increased free radical production by iso (Rajadurai and Prince, 2007).

There was a significant elevation in the level of total serum protein in ALA groups in comparison with control group because ALA preserve the structural integrity of the liver. From the toxic effects (Shay et al 2009).

Blood serum protein is a fairly labile biochemical system, precisely reflecting the condition of the organism and the changes happening to it under influence of internal and external factors. High serum protein levels have been reported due to improve liver and other organs functions which synthesized plasma protein (Kim et al, 1999).

ALA administration resulted in increase of serum total protein by preventing protein oxidation in these results, serum total protein and albumin were significantly increased and that may be due to its ability of to scavenge free radicals (Lachman et al, 2000).

Administration of ALA reverted back these changes to near normal it may be due to the decreased state of protein catabolism and induced a direct positive effect on the synthesis and secretion of albumin (De marko et al, 2005).

Table1: Mean values of serum CK (U/L) in ISO and ALA administrated compared with control group

Groups	3rd week	6th week	9th week
Control	159.30±11.40	163.81±10.79	168.31±10.18
ISO	601.70±19.83**	798.83±22.15**	1118.78±26.15***
Treated	492.81±23.81*	519.75±20.11**	448.01±17.31*
Protected	435.83±16.51*	382.85±11.01*	350.15±15.31*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 2: Mean values of serum CK-MB (U/L) in ISO and ALA administrated group compared with control group

Groups	3rd week	6th week	9th week
Control	217.60±11.10	222.70±9.99	231.81±10.15
ISO	479.81±16.12*	667.83±21.83**	818.79±43.58**
Treated	441.38±12.11*	430.58±16.03*	311.83±11.83
Protected	318.15±6.66	3889.83±10.51	391.75±8.87*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (3) :Mean values of serum CK-MB (U/L) in ISO and ALA administrated group compared with control group

Groups	3rd week	6th week	9th week
Control	497.81±18.15	483±15.39	529.83±11.75
ISO	1331.89±72.31***	1597.83±68.88***	2233.39±71.32***
Treated	801.70±21.53*	732.83±19.77*	653.15±18.75
Protected	501.83±18.31	525.70±11.83	761.81±20.51*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (4) Mean values of serum AST (U/L) in ISO and ALA treated and control group

Groups	3rd week	6th week	9th week
Control	107.83±6.67	115.11±8.11	109.82±7.30
ISO	293.81±7.51**	305.11±9.70**	388.81±10.57**
Treated	272.56±8.31**	161.36±8.89	131.75±7.77
Protected	129.81±4.62	187.7±9.70*	215.81±8.33*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (5) : the mean values of serum glucose legel in control, ISO and ALA treated groups

Groups	3rd week	6th week	9th week
Control	81.31±2.51	79.51±2.31	83.81±2.30
ISO	123.81±3.61*	149.87±5.11*	168.75±5.82*
Treated	90.77±2.38**	119.81±3.75	131.83±4.91
Protected	89.81±2.01	129.18±3.11*	159.81±5.30*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (6) The mean values of Erythrocytes (G6PDH) in control, ISO and ALA administered groups in U/gm HB.

Groups	3rd week	6th week	9th week
Control	7.11±0.39	6.86±0.44	6.99±0.38
ISO	9.12±0.51*	9.99±0.75*	11.75±1.01*
Treated	8.15±0.38	8.11±0.62	8.75±0.54
Protected	8.25±0.73	8.99±0.87*	10.98±0.89*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (7): mean values of Serum Calcium legal in Control, ISO and ALA administrated groups in mg/dL

Groups	3rd week	6th week	9th week
Control	8.71±0.38	8.88±0.42	8.62±0.51
ISO	7.35±0.61*	6.91±0.62*	6.75±1.02*
Treated	8.91±0.36	9.01±0.45	9.00±0.62
Protected	8.16±0.39	6.75±1.20*	6.11±1.13*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (8): mean values of Serum Sodium (mEg/L) in Control, ISO and ALA administrated groups.

Groups	3rd week	6th week	9th week
Control	141.53±3.11	149.81±3.70	151.82±4.11
ISO	111.35±4.75*	101.18±5.70*	109.81±6.82*
Treated	139.82±3.75	124.81±4.17	128.11±3.35
Protected	127.1±5.90	109.75±4.75*	101.81±5.11*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table (9):The mean value of serum Potassium legal in control ISO, ALA treated and protected groups

Groups	3rd week	6th week	9th week
Control	2.84±0.11	2.88±0.21	2.81±0.30
ISO	5.71±0.25*	5.93±0.51*	5.89±0.70*
Treated	3.15±0.70	4.01±0.53	3.87±0.51
Protected	3.75±0.42	4.88±0.78*	5.97±0.91*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table10: The mean values of serum phosphorus legal in mg/dL in control, ISO and ALA administrated groups

Groups	3rd week	6th week	9th week
Control	4.01±0.21	4.12±0.17	4.19±0.33
ISO	6.98±*0.87	8.11±1.11*	7.88±1.21*
Treated	4.31±0.39	4.91±0.81	4.85±0.91
Protected	4.25±0.41	7.39±1.01*	8.38±1.12*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 11: The mean value of heart tissues (SOD) in (U/gm tissues) in control , ISO and ALA administered groups

Groups	3rd week	6th week	9th week
Control	44.31±2.35	40.75±3.11	38.75±1.97
ISO	30.75±2.22*	26.15±3.01*	20.10±1.98*
Treated	45.61±3.15	41.31±2.77	40.11±3.03
Protected	41.63±2.54	33.81±2.23*	21.81±2.01*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 12: Mean values of cardiac muscle CAT in control, ISO and ALA administrated group

Groups	3rd week	6th week	9th week
Control	51.75±4.44	55.31±3.51	49.88±3.16
ISO	28.81±2.11**	23.81±3.51**	18.75±2.11**
Treated	48.71±3.45	54.87±3.75	39.51±2.75
Protected	45.75±3.33	32.81±2.75*	21.06±3.01*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 13: The mean value of Cardiac muscles L-MDA in control, ISO and ALA administered groups

Groups	3rd week	6th week	9th week
Control	0.77±0.03	0.83±0.11	0.89±0.12
ISO	2.70±0.13**	3.01±0.25**	4.44±0.39**
Treated	0.88±0.05	0.79±0.03	0.91±0.12
Protected	0.97±0.36	2.33±0.31*	2.97±0.35*

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 14: The mean values of serum total protein gm/dL in control ISO and ALA administered groups

Groups	3rd week	6th week	9th week
Control	6.66±0.43	6.75±0.79	6.77±0.58
ISO	6.98±0.88	7.48±0.93	8.39±0.97*
Treated	5.98±0.75	5.82±0.79	5.18±0.67*
Protected	6.17±0.70	6.73±1.01	7.03±0.93

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

Table 15: The mean values of Serum Albumin in gm/dL in control, ISO and ALA groups

Groups	3rd week	6th week	9th week
Control	4.13±0.52	4.32±0.66	4.40±0.51
ISO	5.11±0.72	5.63±0.86*	5.09±0.92*
Treated	4.39±0.79	4.41±0.82	3.75±0.78
Protected	4.18±0.31	4.38±0.49	4.69±0.81

*** Significant at p<0.05. ** High significant at p<0.01 ***Very high significant at p<0.001**

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