ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

The Cardioprotective Potential of Trimetazidine in Myocardial Ischemia Reperfusion Injury.

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ABSTRACT

The objective of the current study is to assess the possible cardioprote-ctive potential effect of trimetazidine in myocardial ischemia reperfusion injury induced by ligation of coronary artery in a male rat model.28adult male albino rats were randomized into 4 equal groups: (1), *Sham group*, rats underwent the same anesthetic and surgical procedure as the control group except for LAD ligation; (2), *Active control group*, rats subjected to regional ischemia for 30 min by ligation of LAD coronary artery and reperfusion for 2 hours; (3), *Control vehicle group*, rats received DMSO (vehicle of trimetazidine) via IP route and subjected to ischemia for 30 minutes before ligation of LAD coronary artery & reperfusion for 2 hr; (4), *Trimetazidinetreated group,* rats pretreated with trimetazidine5mg/kg via IP injection 30minutes before ligation of LAD coronary artery & then subjected to reperfusion for 2 hr. In control group, as compared with sham, tissue TNF-α, IL-6, IL-10, caspase-3 and BAX, plasma cTn-T and serum MDA significantly increased (P<0.05), while serum GSH significantly decreased (P<0.05). Histopathologically, control group showed a significant cardiac injury (P<0.05) compared with sham group. Trimetazidine significantly counteracted (P<0.05) the increase of TNF-α, IL-6, caspase-3 and BAX and counteracted the increase in plasma cTn-T and serum MDA. Trimetazidine produces a significant elevation (P<0.05) in cardiac IL-10 and serum GSH with significant reduction in (P<0.05) cardiac injury. Trimetazidine attenuates myocardial I/R injury in male rats via interfering with inflammatory reactions and apoptosis which were induced by I/R injury .

Keywords: Myocardial ischemia, reperfusion, inflammatory reactions, Apoptosis.

Abbreviations: LAD (Left Anterior Descending artery), I.P (intraperitoneal), DMSO (dimethyl sulphoxid), MDA (malondialdehyde), GSH (reduced glutathione), TNF-α (Tumor Necrosis Factor alpha), IL-6 (Interleukin 6), IL-10 (Interleukin 10), caspase-3 (cysteine aspartic acid-protease 3), BAX (bcl2 associated X protein), cTn-T (cardiac troponin T), MI/R (myocardial ischemia reperfusion).

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ISSN: 0975-8585

INTRODUCTION

Ischemia and reperfusion (I/R) is a pathological condition characterized byan initial restriction of blood supply to an organ followed by the subsequent restoration of perfusion and concomitant reoxygenation [1].Prolonged organic ischemia is characterized by insufficient oxygen supply resulting in tissue ATP depletion with a transition to activation of anaerobic metabolic pathways which cannot maintain cellular function for prolonged periods lastly leading to cell death[2].The acidosis that ensues obliges the cell to eliminate excess hydrogen ion via the Na+/H+ exchanger. By movement of Na+ into the cell and H+ out of the cell. Surplus Na+ is removed via the Na+/ Ca2+exchanger and leads to significant increases in intracellular Ca2+. Consequently the high intracellular Ca^{2+} concentration promotes apoptosis. Excess Ca2+ ion leads to excessive inflow of water, give rise to the opening of the MPTP and mitochondrial swelling [3].Mitochondrial permeability transition pore (MPTP) shows a crucial role in reperfusion injury. Opening of the channel causes deep and usually irreversible changes in mitochondrial bioenergetics and leads to the start of mechanisms causing necrosis and apoptosis of cardiomyocytes [4].Within myocardial ischemia, tissue pH significantly declines and returns to normal after reperfusion [5]. A difference in metabolic supply and demand within the ischemic organ results in deep tissue hypoxia and microvascular dysfunction [6]. Neutrophils induce inflammatory mediators that amplify recruitment of neutrophil in the ischemic-reperfused myocardium, so expanding myocardial damage[7].Myocardial ischemia is differentiated with anaerobic metabolism and intracellular acidosis[8].During reperfusion, the electron transport chain is reactivated, generating Reactive oxygen species(ROS). ROS mediate myocardial reperfusion injury by inducing the opening of the MPTP, acting as a neutrophil chemoattractant. Several hours after the onset of myocardial reperfusion, neutrophils accumulate in the infarcted myocardial tissue in response to the release of the chemoattractants ROS, cytokines, and activated complement [9].Actually the reperfusion can be more injurious than the pre-reperfusion ischemia [8]. Trimetazidineselectively inhibit the mitochondrial long-chain 3-ketoacyl coenzyme A (CoA) thiolase in the myocardium. As a result, trimetazidine lessens the detrimental effects of free fatty acid-associated oxidative stress. Studies demonstrated that mechanism of trimetazidine mediated by triggering of p38 mitogen-activated protein kinase (MAPK) and Akt signaling.Trimetazidine is an anti-apoptotic drug through decreasing caspase-3 levels [10].Trimetazidine indirectly interacting with free radicals via activation of antioxidants enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX)[11]. Trimetazidine is also a useful as anti-inflammatory drug via suppressing the induction of cytokines such as TNF-α [12].

MATERIALS AND METHODS

Pure trimetazidine powder(99%) (Santa crus, USA),normal saline (KSA) ketamine (Hikma, Jordan), Xylazine (RompunTM, 2% vials, Bayer AG, Leverkusen, Germany). Rat tumor necrosis factor-α (TNF-α), (IL-6), (IL-10), caspase3, BAX and cTnT (ELISA) kits were purchased from Biotangusa, USA. Trichloroacetic acid (TCA)Merck-Germany, Ethylene diaminetetraacetic acid disodium (EDTA)BDH, U.K. Thiobarbituricacid (TBA) Fluka company, Switzerland 5,5-Dithiobis (2-nitrobenzoic acid) DTNB Sigma company Ltd. Reduced glutathione Biochemical, USA and Methanol Fluka company, Switzerland. regarding instruments , High Intensity Ultrasonic Liquid Processor (Sonics & materials Inc., USA), Digital Spectrophotometer EMCLAB/ Germany, Bio-Elisa Reader,BioTek Instruments, USAand ventilator (Harvard. USA).

Animal

After the approval that has been established by the Institutional Animal Care and Use Committee (IACUC) and submission the required applications, 28 male albino rats weighting (180-300 g) were purchased from Animal Resource Center. They were housed in the animal house (for one week) in a temperature-controlled (25°±1C) room (humidity was kept at (60–65%) with alternating 12-h light/12-h dark cycles and were allowed to access freely regarding water and chow diet until the time of starting the experimental study .

Study design

After the 1st week of accommodation, the 28 rats were randomly dividedinto 4 groups (7 rats in each) as follow :

1- (Sham group): Rats underwent the same anesthetic and surgical procedures but without ligation for the LAD .

2- Active control (MI/R) group: rats followed surgical operation for LAD ligation and they were subjected to 30 min of ischemia and 120 min of reperfusion.
3- (MI/R) + Vehicle pretreated group: rats were pretreated with DMSO via intraperitoneal injection 30 minutes before ligation of LAD**,** then underwent surgical LAD ligation, and subjected to 30min of ischemia followed by 120 min of reperfusion.
4- (MI/R) + trimetazidine pretreated group: rats of this group take a single I.P injection of trimetazidinein a concentration of 5 mg/kg dissolved in 0.5% DMSO 30 minutes immediately before ligation of LAD, then subjected to surgical LAD ligation with 30 minutes of ischemia followed by 120 min of reperfusion[13].

Surgical ligation of the LAD

Rats were anesthetized with (IP) injection of 100 mg/kg ketamine and 10 mg/kg Xylazine [17]. After intubation of the trachea by a 20 G cannula and the endotracheal tube was connected tightly to the ventilation machine. The ventilation rate was fixed from 120-135 breath/minute with tidal volume 20 ml/kg body weight, with 100% oxygen. Pericardial layer incision was made by administration round end scissors to open the space. The LAD coronary artery was transient ligated 1 to 2 mm below the tip of the left auricle using a tapered needle and a 8-0 polypropylene ligature. Tightening the ligature could thenocclude the artery for a 30-minute ischemic period [18]. The chest cavity was closed by bringing together the fourth and fifth ribs with one 2-0 silk suture.Cardiac reperfusion was achieved byreleasing the tension applying to the ligature for 120 minutes [19].The rats were euthanized after reperfusion via injection high dose of anesthesia and the chest was re-opened then the right ventricle was punctured with a syringe needle so that about 3 ml of blood was aspirated for later blood analysis. After that, the heart was isolated and divided into 2 pieces , the apical partused for histological examination and the basal was used for measuring the tissue parameters .

Blood sampling for measurement of plasma cTn-T, serum MDA and serum reduced GSH

At the end of experiment, about 2-3 ml of blood sample was placed in a tube containing disodium ethylene diamine tetra acetic acid (EDTA) (22 mg/mL) as anticoagulant and mixed thoroughly and then centrifuged at 3000 rpm for 15 min then the supernatant was used for determination of plasma cTn-T level,whereas the remaining blood was allowed to clot in an ordinary tube at 37 $^{\circ}$C then it was centrifuged at 3000 rpm for 15 minutes then the supernatant was taken for MDA and GSH serum levels determination.

Tissue preparation for TNF-α, IL-6, IL-10, caspase 3 and BAX measurements

The upper parts of the ventricles were washed with cold normal saline to remove any blood, stored in deep freeze (-20˚C), and then homogenized with high intensity liquid processor in 1:10 (w/v) phosphate buffered saline that contain 1% triton X-100 and protease inhibitor cocktail [17].The homogenate was centrifuged at 14000 rpm 4˚Ċ for 20 min. The supernatant was collected for determination of TNF-α, IL-10, IL-6, Bax, and Caspase- by ELISA with a commercially available ELISA kit (Literature of kit by life Diagnostic, USA) according to the manufacturer's instructions.

Preparation for Histopathology

The apical parts of the heart were excised immediately, rinsed using ice-cold 0.9% saline and fixed in 10% formalin solution pH 7.4 [18] embedded in paraffin wax. The paraffin-embedded tissues were sectioned (4-µm thick), stained with hematoxylin and eosin (H&E). Damage scores were evaluated according to the following morphological criteria that have been used to evaluate the histopathological damage [19] as follow:

Score 0, no damage; score 1 (mild), interstitial edema and focal necrosis; score 2 (moderate), diffuse myocardial cell swelling and necrosis; score 3 (severe), necrosis with presence of contraction bands and neutrophil infiltrate; score 4 (highly severe), widespread necrosis with presence of contraction bands, neutrophil infiltrate, and hemorrhage.

Statistical analyses

Data were expressed as mean ± SEM. An expert statistical advice was considered for data analysis which were aided by computer. Statistical analysis were done using SPSS version 20.0 computer software

ISSN: 0975-8585

(Statistical Package for Social Science). ANOVA (analysis of variance) had been used for measurement (numerical data). Mann-Whitney test had been used for myocardial damage score. P value <0.05 regarded as significant.

RESULTS

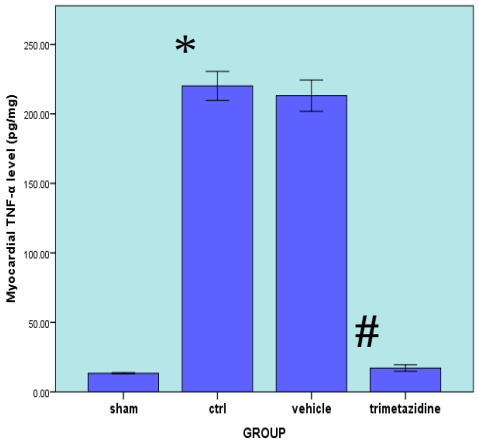

Figure 1: The mean of myocardial TNF-α (pg/mg) in the four experimental groups at the end of the experiment.*P<0.05 *vs*.sham; # P<0.05 *vs*. Ctrl group.

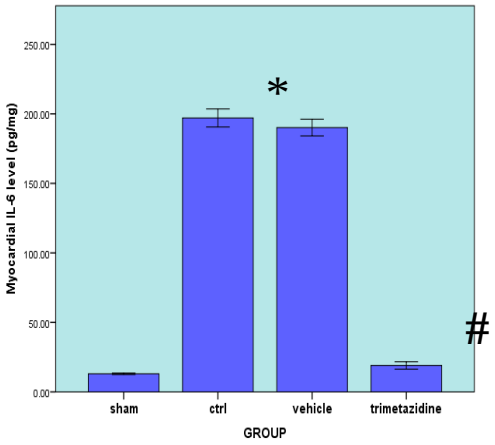

Figure 2. The mean of myocardial level IL-6 (pg/mg) in the four experimental groups at the end of the experiment. *P<0.05 *vs*. sham group; #P<0.05 *vs*. Ctrl group.

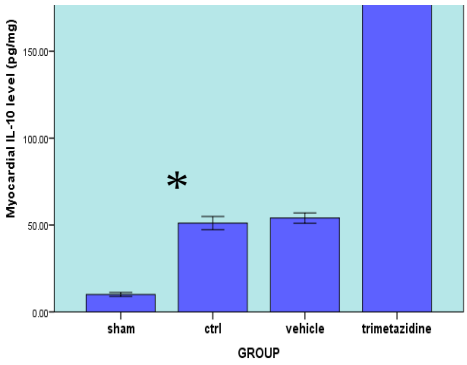

Figure 3: The mean of myocardial IL-10 (pg/mg) in the four experimental groups at the end of the experiment.*P<0.05 *vs*.sham; # P<0.05 *vs*. Ctrl group.

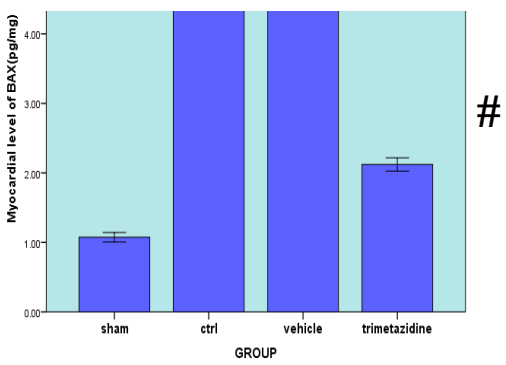

Figure 4. The myocardial mean ofBAX (pg/mg) in the four experimental groups at the end of the experiment. *P<0.05 *vs*. sham group; # P<0.05 *vs*. Ctrl group.

ISSN: 0975-8585

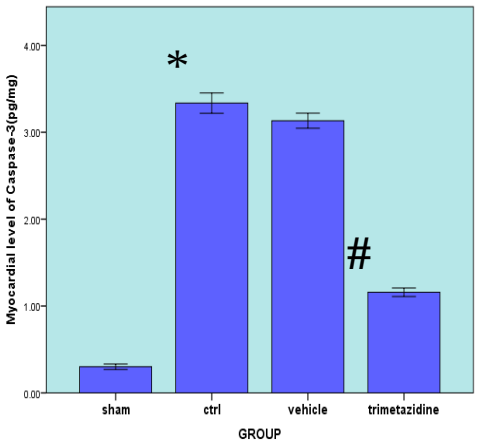

Figure 5. The myocardial mean ofCaspase-3 (pg/mg) in the four experimental groups at the end of the experiment. **P*<0.05 *vs*. sham group, # *P*<0.05 *vs*. Ctrl group.

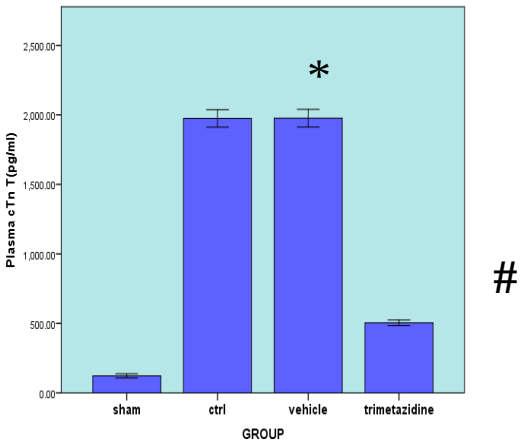

Figure 6. The mean of plasma cTn-T level (pg/ml) in the four experimental groups at the end of the experiment. *P*<0.05 vs. sham group, # *P*<0.05 vs.Ctrl group.

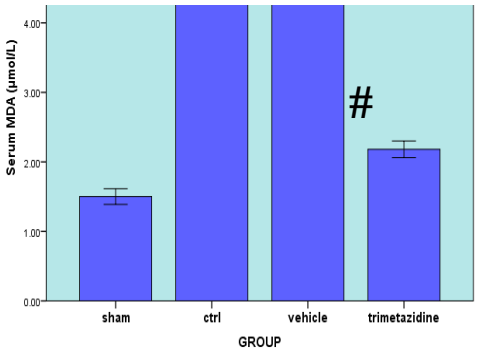

Figure 7. The myocardial mean of MDA (μmol/L) in the four experimental groups at the end of the experiment. **P*<0.05 *vs*. sham group, # *P*<0.05 *vs*. Ctrl group.

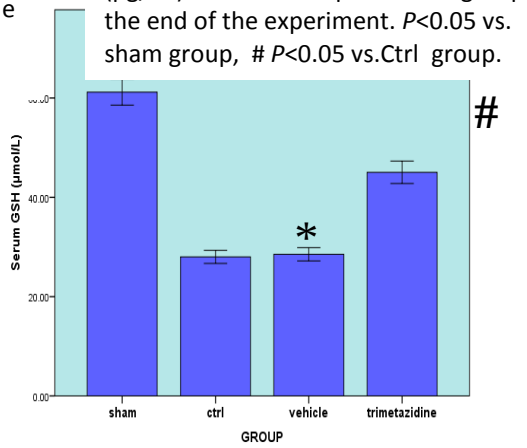

Figure 8. The myocardial mean of GSH (μmol/L) in the four experimental groups at the end of the experiment. **P*<0.05 *vs*. sham group, # *P*<0.05 *vs*. Ctrl group.

Table 1: Comparison according to Mann-Whitney test for scoring regarding histopathological changes

GROUP	P value
1.Sham	
2. Control	<0.05*
3. Trimetazidine	<0.05#*

ISSN: 0975-8585

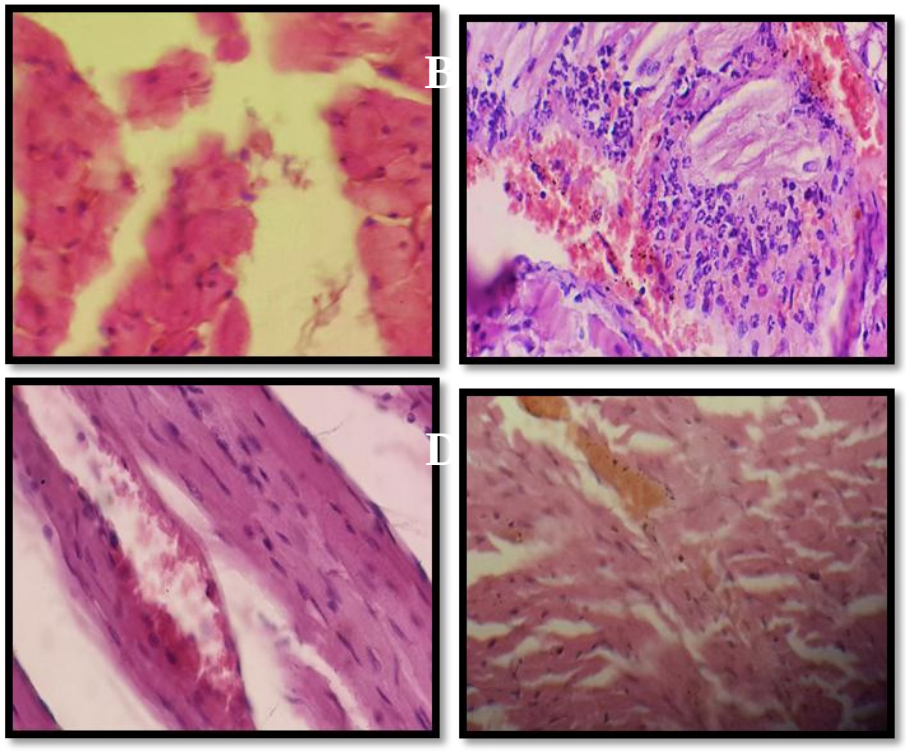

Figure 9: Representative photomicrograph of a section of the heart tissue section stained with Haematoxylin and Eosin (X 40). A)The control group showing hemorrhage ,interstitial edema, necrosis and neutrophil infiltration .B) The sham group showing normal architecture C) The vehicle group showing sever hemorrhage and extravasation of RBC, presence of sever interstitial edema, presence of neutrophil infiltration and necrosis. D) The Trimetazidine pretreated group showing near normal cardiac tissue with absence of edema, absence of neutrophil infiltration, absence of necrosis, and only congested capillary structure.

Biochemical results

Effect on Pro-inflammatory cytokines (TNF-α and IL-6): Results revealed a significant increase (P<0.05) in (TNF-α and IL-6) cardiac tissue levels in the MI/R group as compared with the sham group, while in the MI/R + trimetazidine pretreated group, trimetazidine produce a significant decrease (P<0.05) in the (TNF-α and IL-6) cardiac tissue levels as compared with the MI/R group as shown in table 1 and figures1 and 2.

Effect on anti-inflammatory cytokine (IL-10). Results revealed a significant increase (P<0.05) in (IL-10) cardiac tissue level in the MI/R group as compared with the sham group, while in the MI/R +trimetazidinepretreated group, trimetazidineproduce a significant elevation (P<0.05) in the (IL-10) cardiac tissue level as compared with all other groups (sham group, the MI/R group and MI/R +vehicle group as shown in table 1 and figure 3.

Effect on apoptotic markers (caspase-3 and BAX). Results revealed a significant increase (P<0.05) in (caspase-3 and BAX) cardiac tissue levels in the MI/R group as compared with the sham group, while in the MI/R + trimetazidinepretreated group, trimetazidineproduce a significant reduction (P<0.05) in the (caspase-3 and BAX) cardiac tissue levels as compared with the MI/R group as shown in table 1 and figures 4 and 5.

Effect on Plasma Level of Troponin T (cTnT). Results revealed a significant increase (P<0.05) in (cTnT) plasma level in the MI/R group as compared with the sham group, while in the MI/R + trimetazidinepretreated group, trimetazidineproduce a significant reduction (P<0.05)in the (cTnT) plasma level as compared with the MI/R group as shown in table 1 and figure 6.

Effect on the serum level of oxidative stress markers (MDA and GSH). Results revealed a significant increase (P<0.05) in the serum level of MDA in the MI/R group as compared with the sham group, while in the MI/R +trimetazidinepretreated group, trimetazidineproduce a significant reduction (P<0.05) in MDA serum level as compared with the MI/R group. Concerning GSH, results revealed a significant decrease (P<0.05) in the serum

level of GSH in the MI/R group as compared with the sham group, while in the MI/R +trimetazidinepretreated group, trimetazidineproduce a significant increase (P<0.05) in GSH serum level as compared with the MI/R group as shown in table 1 and figures 7 and 8.

Histopathlogical Findings

Histologically, the MI/R group revealed a significant cardiac tissue injury (P<0.05) compared with the sham group, and this injury was showing sever hemorrhage, presence of interstitial edema, necrosis and neutrophil infiltration in contrast with the cross section of the sham group which showed a 100% normal structure of cardiac tissue with no interstitial edema, no diffuse myocardial cell swelling and necrosis, no neutrophils infiltration, no hemorrhage, no capillary compression and no evidence of apoptosis. Treatment of rats with trimetazidine significantly decrease (P<0.05) the injury of cardiac tissue and cross section from this group (MI/R+trimetazidine) showed near normal cardiac tissue with absence of edema, absence of neutrophil infiltration, absence of necrosis, and only congested capillary structure while there was no significant difference between the MI/R and MI/R +vehicle groups as shown in figures 9 A, B, C, D.

DISCUSSION

The common origin of myocardial infarction is occlusion of the coronary artery as a result of the embolization of an unstable coronary plaque [20]. Activation of Polymorphonuclear cell(PMN's), eicosanoids, cytokines, ROS and complement products have been shown to be involved in the initial ischemic period [21].The intracellular and extracellular accumulation of these products triggers homeostatic pathways involving necrosis, apoptosis and inflammationthat initially occur during acute myocardial infarction. The apoptotic response may then lead to potential permanent tissue or end organ dysfunction. Restoration of blood flow to ischemic myocardium is the current therapy, yet is associated with ischemia/reperfusion injury[22].

Effects of Trimetazidine on pro-inflammatory cytokines (TNF-α and IL-6) and on the anti-inflammatory cytokine (IL-10).

Pretreatment with trimetazidinebefore induction of myocardial ischemia produced a significant reduction (P<0.05) in the myocardial tissue levels of pro-inflammatory cytokines (TNF-α, IL-6), with the significant elevation (P<0.05) in the level of anti-inflammatory cytokine IL-10 compared to control. Kuralay et al., (2006)reported in their study that patients receiving trimetazidine prior to percutaneous transluminal coronary angioplasty (PTCA) had significantly decreased level of TNF- α during initial 48 h after PTCA and it is known that PTCA triggers systemic inflammatory response by inducing ischemia reperfusion cycle through repeated balloon inflation which can be followed by tissue injury and impaired anti-oxidant status [12].Martins et al., (2012)showed that interleukin 6 levels were significantly lower in the trimetazidine treated group as compared with those in the control group in patients submitted to coronary artery bypass graft (CABG)[23].

There is no data yet available on effect of trimetazidine on anti-inflammatory cytokine, IL-10 in myocardial ischemia reperfusion injury.

Effect of Trimetazidine on Caspase 3 and BAX

The level of caspase 3 and BAX in cardiac tissue was significantly decreased (P<0.05) in thetrimetazidinepretreated group compared to the control group. Xu et al., (2012) indicated that the expression of pro-apoptotic protein Bax was down-regulated in the trimetazidine group, compared with acute myocardial infarction (AMI) control group[24]. Khan et al., (2010) showed that trimetazidine -treated group decreased caspase-3 expression compared to the I/R group when administrated at the onset of reperfusion in rat model of myocardial ischemia-reperfusion [10].

Effect of trimetazidine on cTnT level

The cTnT plasma level of trimetazidinepretreated group was significantly decreased (P<0.05) compared to the control group.

Iseken et al., (2009) observed that pretreatment with trimetazidine showed some beneficial effects in decreasing myocardial injury. Postoperative levels of troponin T was significantly lower in the trimetazidine group than in the control group[25]. Martins et al., (2011) found that the value of Troponin T was significantly lower in the group undergoing pre-treatment with trimetazidine compared the placebo group, suggesting a reduction of the aggression by reperfusion on the myocardium[26].

Effect of trimetazidine on MDA and reduced GSH level

There was a significant decrease (P<0.05) in serum MDA level with a significant elevation (P<0.05) of GSH serum level in the trimetazidinepretreated group compared to the active control group. Vaillant et al., (2008) found thattrimetazidine increased the ventricular fibrillation threshold (VFT) and decreased both MDA blood levels (an index of lipid peroxidation) and the ischemic area in myocardial ischemia that induced after thoracotomy by complete, but brief (1 min) occlusion of the left anterior descending coronary artery under electrical stimulation[27].

To best of our knowledge, there is no study measured the effect of trimetazidine on reduced GSH level in myocardial ischemia reperfusion injury**.** Treatment of rats withtrimetazidinesignificantly reduce cardiac injury (P< 0.05) as compared with active control group. The scores of the control group demonstrates a 28.5% with highly severe myocardial injury and 71.5% with sever myocardial injury, while the score of trimetazidinetreated group were 14.25% of the group had no damage, 71.5% had mild cardiac injury and 14.25% had moderate cardiac injury.Kutalaet al (2006) proved that pretreatment of hearts with trimetazidine significantly enhanced the recovery of heart function and decreased infarct size in myocardial ischemia reperfusion injury[28].Steg et al (2001)proved that trimetazidine limits infarct size, decreases platelet aggregation, and reduces leukocyte influx into the infarct zonein patients treated by primary angioplasty for acute myocardial infarction [29].

CONCLUSION

It can be concluded that pretreatment with trimetazidine modulates myocardial ischemia reperfusion injury via interfering with inflammatory, oxidative pathways and apoptosis.

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