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Original Article

Protective effect of tacrolimus on myocardial ischemia/reperfusion injury in rats

Takrolimusun sıçanlarda miyokardiyal iskemi / reperfüzyon hasarı üzerindeki koruyucu etkisi

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Abstract

Aim: Acute myocardial infarction is a major cause of morbidity and mortality worldwide. Although thrombolytic therapy and primary percutaneous coronary intervention are the therapeutic approaches to reduce the myocardial ischemic injury and limit the infarct size by providing reperfusion, process can itself induce cardiomyocyte death known as myocardial reperfusion injury. In addition to effects on immunsuppression for organ transplantation, tacrolimus has diverse actions that result in amelioration of ischemia/reperfusion (I/R) injury. In this study, we aimed to evaluate the effects of tacrolimus on myocardial I/R injury in rats.

Material and Methods: Adult male Wistar albino rats (n=18; mean weight, 252±20 g; age, 46-54 days) were included to this study. Rats were randomly assigned into three groups: Group 1 (sham, n=4), Group 2 (I/R+saline, control, n=7), Group 3 (tacrolimus+I/R, n=7). Tacrolimus (0.1 mg/kg) was administered as an intravenous infusion in the first 15 min of reperfusion after 45 min ischemia period.

Results: Although there were no change in area at risk, infarct size was markedly reduced in tacrolimus group when compared to control group ($p<0.05$). Histopathological parameters (myofibrillar edema, myocytolysis, focal hemorrhage and polymorphonuclear leukocyte infiltration) were markedly increased in I/R control group, and significantly reduced by tacrolimus treatment ($p<0.05$). However, there were no marked changes in biochemical analysis.

Conclusion: This study demonstrated that tacrolimus showed cardioprotective effects in myocardial I/R injury in rats.

Keywords: tacrolimus; occlusion; reperfusion; infarct size; myocardial

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ÖZ

Amaç: Akut miyokard enfarktüsü, dünya çapında önemli bir morbidite ve mortalite nedenidir. Trombolitik tedavi ve birincil perkütan koroner müdahale, miyokardiyal iskemik hasarı azaltmak ve reperfüzyon sağlayarak enfarktüs boyutunu sınırlamak için terapötik yaklaşımlar olsa da, sürecin kendisi miyokardiyal reperfüzyon hasarı olarak bilinen kardiyomiyosit ölümüne neden olabilir. Organ transplantasyonu için immün baskılama üzerindeki etkilerine ek olarak, takrolimus, iskemi / reperfüzyon (İ / R) hasarında iyileşme ile sonuçlanan çeşitli etkilere sahiptir. Bu çalışmada, takrolimusun sıçanlarda miyokardiyal İ / R hasarı üzerindeki etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Erişkin erkek Wistar albino sıçanlar (n = 18; ortalama ağırlık, 252 ± 20 g; yaş, 46-54 gün) bu çalışmaya dahil edildi. Sıçanlar rastgele üç gruba ayrıldı: Grup 1 (şam, n = 4), Grup 2 (İ / R + salin, kontrol, n = 7), Grup 3 (takrolimus + İ / R, n = 7). Takrolimus (0,1 mg / kg) 45 dakikalık iskemi süresinden sonra reperfüzyonun ilk 15 dakikasında intravenöz infüzyon olarak uygulandı.

Bulgular: Risk altındaki alanda değişiklik olmamasına rağmen, kontrol grubuna göre takrolimus grubunda infarkt boyutu belirgin şekilde azaldı (p <0,05). Histopatolojik parametreler (miyofibriler ödem, miyositoliz, fokal kanama ve polimorfonükleer lökosit infiltrasyonu) İ / R kontrol grubunda belirgin şekilde artmış ve takrolimus tedavisi ile önemli ölçüde azalmıştır (p <0,05). Bununla birlikte, biyokimyasal analizde belirgin bir değişiklik olmadı.

Sonuçlar: Bu çalışma, takrolimusun sıçanlarda miyokardiyal İ / R hasarında kardiyoprotektif etkilere sahip olduğunu göstermiştir.

Anahtar kelimeler: takrolimus; oklüzyon; reperfüzyon; infarct boyutu; miyokardiyal

Introduction

Myocardial ischemia/reperfusion (I/R) injury leads to severe arrhythmias and associated with high risk of mortality [1]. Accumulation of reactive oxygen species and cardiomyocyte apoptosis play a role in the pathogenesis of myocardial I/R injury [2]. Inflammatory cascade is activated with reperfusion and cardiomyocyte death and apoptosis occur during this period. Although percutaneous coronary intervention (PCI) has a positive effect on survival of patients with acute myocardial infarction (AMI), there is evidence suggesting that PCI increases the heart failure risk in patients with AMI, as it leads to myocardial I/R that result with myocardial injury and cardiomyocyte death [3]. Thus, novel therapeutic aproaches are needed for preventing myocardial I/R injury.

Tacrolimus, also known as FK506, is a calcineurin inhibitor, and acts as an immunsuppresive agent. It is used typically in organ transplantations to reduce the risk of graft rejection and autoimmune diseases [4]. Several studies have revealed that tacrolimus has an antioxidative and antiapoptotic effects [5]. It blocks the catalytic activity of calcineurin and this leads to gene repression that regulates the production of adhesion molecules and cytokines. Due to this repression with tacrolimus, inflammatory cell response, platelet activation, neutrophil adhesion and aggregation decrease in I/R injury [6].

In this study, we aimed to investigate the protective effect of tacrolimus on myocardial I/R injury in a rat model by using hemodynamical, histopathological, and biochemical evaluations.

Material and Methods

Animals

Adult male Wistar Albino rats (mean weight, 252±20 g; age, 46-54 days) were included to this study. Rats were housed in a climate-controlled room (temperature 25±2oC; humidity 50-60%) on a 12 h light/dark cycle and ad libitum access to food and water. All the study protocols were approved by the Institutional Animals Ethics Committee of Dokuz Eylul University with the decision date and no; 08/04/2005-05/06/14-29. The investigation conformed with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No.85-23, revised 1996).

Study Groups

Rats were randomly assigned into three groups: Group 1 (sham, n=4), Group 2 (I/R+saline, control, n=7), Group 3 (tacrolimus+I/R, n=7). Tacrolimus (0.1 mg/kg body weight; Prograf R ampul, Fujisawa Pharmaceutical Co., Japan) was administered as an intravenous infusion in the first 15 min of reperfusion after 45 min ischemia period [7]. Rats in the control group were administered with the same volume of saline.

Anesthesia and Monitorization

Ketamine (Ketalar R flacon, 100 mg/ml, Alfasan International, Holland) 35 mg/kg and xylazine (Alfazyne R, 20 mg/ml, Alfasan International, Holland) 5 mg/kg were used for anesthesia. Entubation was performed via tracheostomy. Mechanical animal respiratory vehicle (Ugo Basile SRL, Rodent Ventilator, Italy) was used with the 100% O2 support, 15 ml tidal volume, and respiratory rate of 60/min. Carotid artery was catheterized with 24 G branule for continous pressure monitorization and jugular vein was catheterized with the same way for saline and tacrolimus administration. Heart rate and blood pressure were followed continously by using ECG-pressure monitore during the operation and data were recorded. During the experiment, body temperature was kept at 37°C with the use of a desk lamp.

Surgical Procedure

Left thoracotomy was performed to reach the heart. Following the exploration of the heart, 600 IU/kg heparin sodium (Nevparin R vial, 5000 IU/ml, Mustafa Nevzat Pharmaceutical Company, Turkey) was given intravenously to prevent thrombosis in the coronary artery at the begining of the 15 min hemodynamic stabilization period. After that, 6/0, 10 mm atraumatic prolene suture with snare tape was used for left anterior descending artery (LAD) occlusion. Ischemia was achieved by tightening the snare. Duration of ischemia was 45 min. Reperfusion was initiated by releasing the snare. Successful occlusion was confirmed by a reduction in arterial blood pressure. Reperfusion continued for 3 hours. After sacrification, the heart was removed and sent to pathology laboratory within icy water immediately. Sham group was underwent a similar surgical procedure wherein coronary artery was not occluded.

Calculation of Area at Risk and Infarct Size

Cardiac area at risk and infarct size determination was performed as described previously [8]. At the end of experiments, the left anterior descending coronary artery was occluded again at the same site as previously, and 3 ml of a 2% solution of Evans blue dye was infused into the jugular vein catheter to distinguish between perfused and non-perfused (area at risk) sections of the heart. The Evans blue solution stains the perfused myocardium, while the occluded vascular bed remains uncoloured. Then the heart was excised. Both atria and the roots of the great vessels were removed. The entire ventricle was cut, from the apex to the base, into slices of 3–4 mm, the right ventricular wall was removed, and the area at risk (pink) was separated from the non-ischemic (blue) area. The area at risk was cut into small pieces and incubated with a 1% solution of 2,3,5-triphenyltetrazoliumchloride (TTC, in 20 mM phosphate buffer, pH 7.4) stain for 30 min at 37oC, to visualize the infarct area. The area at risk of infarction was colored brick red, and the infarcted area within the region at risk remains pale yellow (i.e. necrotic area). To fix the color difference in the sections after the procedure, tissues were kept in 10% formalin solution in 20 min, and the field was analyzed by transferring the images to the computer with the help of video image (Image Pro-plus-Media Cybernetics, Silver Spring, Maryland, USA). The ischemic damage area of the myocardium was measured using a morphometric program for each heart slice, and averages of these measurements were presented.

Biochemical Measurements

Intracardiac blood samples were collected at the end of the experiment. The samples were centrifuged at 2400 g, 4oC, for 15 min, and the serum was removed and stored at -80oC until assayed. Immulite R Turbo CKMB (EURO/DPC Ltd. UK) kit was used for creatine kinase MB (CK-MB) levels. Arterial blood samples (0.2 ml) were obtained with an injector containing heparinized saline (20 IU/ml) for blood–gas analysis (pH, pO2, pCO2, and hematocrit) via an arterial cannula in the right common carotid artery at the end of the experiment. The samples were analyzed immediately in a blood–gas analyzer (Irma TruPoint Blood Analysis System, ITC Med, CA, USA).

Histopathological Examination

The sections that were sliced from apex to the bottom into four pieces for the calculation of the infarct area were processed with hematoxylin-eosin while they were kept in 10% formalin solution. Myofibrillar edema, myocytolysis, focal hemorrhage and polymorphonuclear leukocyte (PMNL) infiltration were examined using light microscope after this procedure, and pathological scoring was performed as: 0-none, 1-mild, 2-moderate, 3-severe.

Statistical Analysis

All data are expressed as means±S.E.M. or the percentage incidence. Statistical analyses were performed using SPSS 13.0 for Windows program. Statistical analysis between two experimental groups was performed using a Student's t test. Statistical comparison of more than two groups was performed by a one-way analysis of variance followed by Student–Newman–Keuls multiple comparisons test. The Mann–Whitney U-test was used to detect significant differences between histopathological scores. In all tests, p values less than 0.05 were considered to be statistically significant.

Results

Tables 1 and 2 summarize mean arterial blood pressure and heart rate in all groups, respectively.

Occlusion of the LAD coronary artery produced a marked decrease in blood pressure. Tacrolimus had no marked effect on mean arterial blood pressure and heart rate. There were no marked differenes in pH, pO2, pCO2, and hematocrit values between the groups as shown in Table 3. Additionally, no significant change in CK-MB levels was observed (Table 3).

Area at risk and infarct size in myocardial sections of control and tacrolimus groups was shown in Figure 1. Although there were no change in area at risk, infarct size was markedly reduced in tacrolimus group when compared to control group.

Histopathological evaluations of all groups were presented in Table 4. Myofibrillar edema, myocytolysis, focal hemorrhage and PMNL infiltration were markedly increased in I/R control group when compared to sham group. Tacrolimus significantly attenuated these parameters (Table 4).

Table 1. Mean arterial blood pressure values (mmHg) during coronary occlusion and reperfusion in anesthetized rats

Groups	n	Baseline	Ischemia		Reperfusion	
			1 min	45 min	60 min	180 min
Sham	4	83.8±3.7	-	-	-	-
I/R control	7	86.2±3.1	68.6±2.5*	53.3±1.5*	44.5±2.8*	43.3±2.8*
Tacrolimus + I/R	7	88.7±3.8	70.6±4.0*	57.4±3.9*	60.7±5.0*	51.9±4.9*

I/R, ischemia/reperfusion; *P<0.05 when compared to baseline values.

Table 2. Heart rate values (beats/min) during coronary occlusion and reperfusion in anesthetized rats

Groups	n	Baseline	Ischemia		Reperfusion	
				45 min	60 min	180 min
Sham	4	220.0±17.8	-	-	-	-
I/R control	7	210.2±14.1	204.3±13.1	226.4±9.0	262.1±8.7*	272.1±13.9*
Tacrolimus + I/R	7	209.2±15.9	203.7±17.5	210.6±13.6	224.3±12.7	233.6±7.8

I/R, ischemia/reperfusion; *P<0.05 when compared to baseline values.

Table 3. Biochemical values of the groups

Parameters	Sham (n=4)	I/R control (n=7)	Tacrolimus + I/R (n=7)
CK-MB (U/ml)	1.19±0.15	1.27±0.10	1.18±0.14
Ph	7.38±0.03	7.44±0.02	7.46±0.03
Hematocrit (%)	33.00±3.06	31.57±1.39	32.43±1.95
pO2	90.00±7.86	97.29±6.91	89.71±10.78
pCO2	35.33±3.71	29.43±1.77	31.29±0.71

CK-MB, creatine kinase MB

Table 4. Histopathological grading values of the groups

Parameters	Sham (n=4)	I/R control (n=7)	Tacrolimus + I/R (n=7)
Myofibrillar edema	0.8	1.3	0.9
Myocytolysis	0.0	0.4	0.0
Focal hemorrhage	0.0	0.3	0.3
PMNL Infiltration	0.0	1.6	0.7
Total	0.8±0.2	3.6±0.3*	1.9±0.2*,+

Values are expressed as means and total is given as sum ± SEM. *P<0.05 vs. sham group; +P<0.05 vs. I/R group; PMNL, polymorphonuclear leukocyte; I/R, ischemia/reperfusion

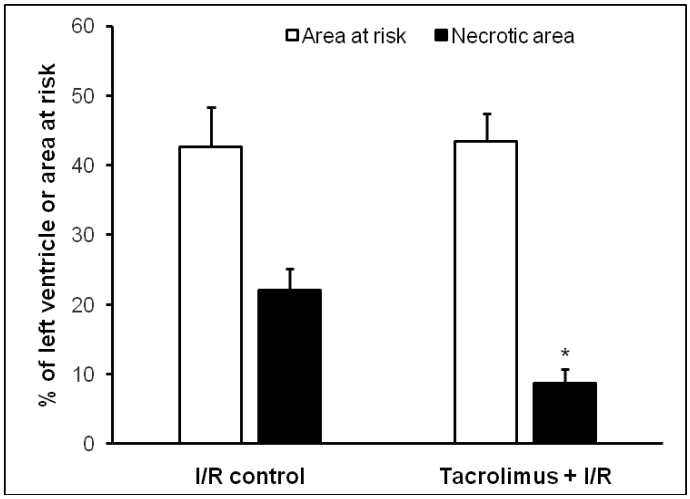

Figure 1. Effects of tacrolimus on area at risk and infarct size. Area at risk indexed to total left ventricle (area at risk/total left ventriclex100) and necrotic area indexed to area at risk (necrotic area/area at riskx100) in percentage of wet weight. All values are the means ± S.E.M., n=7. *P<0.05 versus control group.

Discussion

AMI is the major cause of mortality and morbidity worldwide. The purpose of the treatment choices of patients with MI is to reduce acute myocardial ischemic injury and limit MI size by maintaining effective myocardial reperfusion. However, reperfusion can itself cause cardiomyocyte death known as myocardial I/R injury [9]. Myocardial I/R injury activates the inflammatory response that involves production of oxidants, activation of complement and infiltration by polymorphonuclear neutrophils [10]. Myocardial necrosis, apoptosis and stunning may ocur as a result of this cascade [11]. Infarct size is the most important indicator of long-term mortality and chronic heart failure, so limiting the extent of necrosis during MI has a vital importance. Studies concerning the therapies that focus on to reduce reperfusion injury are available in the literature [12].

Tacrolimus is an immunosuppressive drug and typically used for organ transplantation, atopic dermatitis, various autoimmun and inflammatory diseases [13]. It shows its effect by inhibiting calcineurin, thus; cytokines, lymphokines and adhesion molecules that play role in immune and inflammatory response are being repressed [14]. Considering the positive effects on anti-inflammatory response, there are various studies about the efficacy of tacrolimus on I/R injury in different organ systems. Ustundag et al. demonstrated the positive effects of tacrolimus in the rat ovary I/R models whereas Stringa et al. studied on intestinal I/R injury in mice [15,16]. Primary dysfunction or non-function after liver transplantation is an important problem and main cause of this situation is I/R injury. Huser et al. indicated that graft preconditioning with low-dose tacrolimus reduces I/R injury after liver transplantation in rats [17]. Similarly, a study designed by Takeich et al. showed the protective effect of tacrolimus on I/R injury of the liver. According to this study, survey time was longer and AST levels were decreased in tacrolimus group when compared to control group [18]. In another study, tacrolimus administered to the rats, that have vasculatic neuropathic pain induced by I/R, showed a higher efficacy on pain than control group according to behavioral pain assessment [13]. Bayer et al. claimed that beside ameliorated oxygenation, the presence of macrophages, neutrophils and T-cell subtypes in the isografts were all less than in tacrolimus treated group than control group on I/R injury in rat lung transplantation model [19]. Sahin et al. presented the protective effects of tacrolimus on rat uteri, exposed to I/R injury. Antioxidant capacity of uterine tissue treated by tacrolimus was found to be higher than control group [20]. Beside these studies, several researchers have examined the effects of tacrolimus on myocardial I/R injury. Sheu et al. detected that tacrolimus reduced in infarct size and preserved of myocardial integrity in mini-pigs [21]. Early administration of tacrolimus via coronary artery preserved left ventricular function in an animal study conducted by Yang et al [22]. Similarly, Nishinaka et al. published an article related to the positive effects of tacrolimus on I/R induced myocardial damage in canine heart [23]. In our study, we have found the similar results in rats by measuring planimetric infarct area which is the main determining factor for the presence and intensity of ventricular remodeling after acute myocardial infarction [24]. Both infarct area and proportion of infarct area to the whole area were prominently less in the tacrolimus administered group than control group. Chua et al. administered the tacrolimus directly into the coronary artery and reported markedly attenuated infarct size in porcine myocardial infarction [25]. We administered tacrolimus via jugular vein in fifteen minutes infusion.

In addition to the administration way, administration time of the tacrolimus can be different but results on its efficacy about myocardial I/R injury are coherent. Feng et al. investigated one of the propabl mechanisms of the protective effect of the tacrolimus on myocardial I/R injury. In that study, tacrolimus administered 15 min before ischemia [26]. In our study, we administered the tacrolimus in first 15 min of reperfusion.

Various mechanisms have been indicated by researchers on myocardial protection of tacrolimus. According to Vafadri et

al, tacrolimus blocks the nuclear factor kappa B (NF-KB) activation in peripheral human T-cells [27]. Li et al. reported that PPAR-gamma/PI3K/Akt pathway is involved in the cardioprotective effects of tacrolimus in myocardial I/R injury. Tacrolimus also significantly alleviates the arrhythmias, suppresses cardiac function impairment, and inhibits the oxidative stress and apoptosis in cardiomyocytes [1].

Although Squadrito and colleagues obtained a result about decreased serum activity of CK in their study related to tacrolimus on myocardial I/R model, we have found no statistically significant difference in all groups in terms of CK-MB. However, our histopathologic results are in agreement with the data presented by Squadrito et al, who showed that tacrolimus limits the PMNL accumulation and protects against myocardial I/R injury in rats [28]. We have found a statistically significant difference in terms of PMNL infiltration between tacrolimus group and control group.

Our findings have shown that there were no statistically significant differences in blood gas parameters including pH, pO2, pCO2, and hematocrit between the groups. Similar results were obtained by Mohebbi and colleagues who showed that there was no change in systemic acid-base status with tacrolimus treatment after 9 days [29].

Conclusion

In conclusion, our data showed that tacrolimus has cardioprotective effects in myocardial I/R injury in rats. Although various studies in different animal models have been published, further clinical studies are required for determining the tacrolimus efficacy on myocardial I/R injury.

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Declaration of conflict of interest

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