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Original Article

Protective effect of cilostazol and rosuvastatin on acute kidney injury-induced lung injury using TNF-α and HIF-1α immunoreactivities

TNF-α and HIF-1α immünreaktivitesi ile silostazol ve rosuvastatinin akut böbrek hasarı ile oluşturulan akciğer hasarı üzerine koruyucu etkileri

Şahin İşcan[1], İsmail Yürekli[1], Fatmagül Kuşku Çabuk[2], Habib Çakır[1], Börteçin Eygi[1], Köksal Dönmez[1], Ali Gürbüz[1]

[1]*Department of Cardiovascular Surgery, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey*
[2]*Department of Pathology, İstanbul Bilim University, Gayrettepe Florence Nightingale Hospital, İstanbul, Turkey*

ABSTRACT

Objectives: This study aims to investigate the effects of preoperative cilostazol and rosuvastatin therapy on isolated kidney ischemia/reperfusison (I/R) injury-induced remote lung reperfusion injury in an experimental model.

Materials and methods: A total of 35 female Sprague-Dawley rats were randomly divided into five groups (n=7). Median laparotomy and a 45-min bilateral kidney ischemia were performed. Oral medications were administered three days before the surgical intervention (20 mg/kg cilostazol, 10 mg/kg rosuvastatin, and 20 mg/kg cilostazol+10 mg/kg rosuvastatin). Lung tissue samples were extracted one day after surgery. Tumor necrosis factor-α (TNF-α) and hypoxia-induced factor-1α (HIF-1α) antibodies were used for immunohistochemical examinations of lung tissues cross-sections.

Results: TNF-α immunoreactivities in I/R+cilostazol, I/R+rosuvastatin and I/R+cilostazol+rosuvastatin groups were found to be decreased significantly, compared to I/R group ($p<0.05$). Lung TNF-α immunoreactivities in I/R+rosuvastatin, and I/R+cilostazol+rosuvastatin groups was found to be increased significantly, compared to control group ($p<0.05$). HIF-1α immunoreactivities in I/R+cilostazol, I/R+rosuvastatin, and I/R+cilostazol+rosuvastatin groups were found to be decreased significantly, compared to I/R group ($p<0.05$). HIF-1α immunoreactivites amoung I/R+cilostazol, I/R+rosuvastatin and I/R+cilostazol+rosuvastatin groups were found similar, compared to control group ($p>0.05$).

Conclusion: Cilostazol and rosuvastatin have prophylactic effects on kidney I/R injury-induced lung reperfusion injury. Their single or combined use for peripheral arterial diseases may be beneficial for patients on perioperative period.

Keywords: Ischemia/reperfusion injury; kidney; lung.

ÖZ

Amaç: Bu çalışmada deneysel bir modelde ameliyat öncesi silostazol ve rosuvastatinin izole böbrek iskemi-reperfüzyon (I/R) hasarı sonrasında oluşan akciğer reperfüzyon hasarı üzerine etkileri araştırıldı.

Gereç ve Yöntemler: Toplam 35 adet dişi Sprague-Dawley sıçan rastgele beş gruba ayrıldı (n=7). Medyan laparotomi ve her iki böbreğe 45 dk. iskemi uygulandı. Cerrahi girişimden üç gün öncesinden başlayarak (20 mg/kg silostazol, 10 mg/kg rosuvastatin ve 20 mg/kg silostazol+10 mg/kg rosuvastation) oral tedaviler uygulandı. Cerrahiden bir gün sonra akciğer dokusu örnekleri alındı. Akciğer çapraz kesit dokularının immünhistokimyasal incelemesi için tümör nekroz faktör-α (TNF-α) ve hipoksi ile indüklenmiş faktör-1α (HIF-1α) antikorları kullanıldı.

Bulgular: TNF-α immünreaktivitesi I/R+silostazol, I/R+rosuvastatin ve I/R+silostazol+rosuvastatin gruplarında, I/R grubuna kıyasla anlamlı düzeyde azalmış tespit edildi ($p<0.05$). Akciğer TNF-α immünreaktivitesi I/R+rosuvastatin ve I/R+cilostazol+rosuvastatin gruplarında, kontrol grubuna kıyasla anlamlı düzeyde artmış olarak bulundu ($p<0.05$). HIF-1α immünreaktivitesi I/R+cilostazol, I/R+rosuvastatin ve I/R+cilostazol+rosuvastatin gruplarında, I/R grubuna kıyasla anlamlı düzeyde azalmış tespit edildi ($p<0.05$). HIF-1α immünreaktivitesi I/R+cilostazol, I/R+rosuvastatin ve I/R+cilostazol+rosuvastatin gruplarında, kontrol grubuyla kıyaslandığında benzer bulundu ($p>0.05$).

Sonuç: Silostazol ve rosuvastinin böbrek I/R ile oluşan uzak akciğer reperfüzyon hasarı üzerinde profilaktik etkileri mevcuttur. Bu ilaçların periferik arter hastalıklarında tek başına veya birlikte kullanımı perioperatif dönemde faydalı olabilir.

Anahtar sözcükler: İskemi/reperfüzyon hasarı; böbrek; akciğer.

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Correspondence: Şahin İşcan, MD. İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi Kalp ve Damar Cerrahisi Kliniği, 35360 Karabağlar, İzmir, Turkey. e-mail: sahiniscan@hotmail.com

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Cardiac and vascular operations always have kidney injury risk. This risk may affect patients' postoperative course and kidney injury may also indirectly cause major organ injuries. Aortic cross clamping, cardiopulmonary bypass time, and peripheral perfusion defects during cardiac surgery process are the factors related to kidney injury. However, mostly acute kidney injuries with peripheral arterial surgical interventions due to direct and indirect ischemia/reperfusion (I/R) of the kidneys are encountered. Clamping of abdominal aorta or renal artery directly cause acute kidney injury. Reperfusion of ischemic extremity causes indirect kidney and lung injuries. Also, reperfusions of bilateral ischemic kidneys cause remote organ reperfusion injury. Reperfusions of ischemic kidneys and inflammatory effect of acute renal deficiency after kidney ischemia cause this remote organ effect. Lung is one of the important organs which affect from reperfusion damage.[1] Reperfusion damage may lead to mechanic ventilation need and, therefore, lung damage affect patients' postoperative morbidity and mortality. Medical therapies which reduce renal and lung I/R injury may be beneficial reducing patients' morbidity and mortality.[2]

Cilostazol is a phosphodiesterase inhibitor. It is in use for the treatment of peripheral arterial disease with vasodilator effects, antiplatelet activities, and anti-inflammatory activities. Rosuvastatin is a potent anti-hyperlipidemic drug. However, it is well-known that statins have anti-inflammatory effects by endothelial nitric oxide system.[3,4] In our previous study, we designed an acute kidney injury model and we showed that cilostazol and rosuvastatin had beneficial effects on preventing direct kidney I/R injury and direct kidney I/R injury-induced heart injury.[5] In the present experimental study, which is the continuation of our previous study, we aimed to investigate the protective effects of oral cilostazol, rosuvastatin, and their combination treatment against renal I/R-induced remote lung injury using immunohistochemical indicators.

MATERIALS AND METHODS

In this study, 35 female Sprague-Dawley rats (weight: 190-250 g; age 3.5 to 4 months) were used between December 2015 and April 2016. The experiments were conducted at Animal Research Laboratory, after the approval of Animal Care and Use Committee. The included rats were randomly divided into five groups (n=7): control group, I/R group, I/R+cilostazol group, I/R+rosuvastatin group, and I/R+rosuvastatin+cilostazol group. The rats were followed in the lab and kept at 20 to 22°C during the study with a-12-hour light and dark rhythm. For feeding the rats, unlimited tap water and standard rodent feed were used ad libitum. The animals used in this study were maintained in accordance with the guidelines of the Committee on Animals and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council [DHEW publ. no. (NIH) 85-23, revised 1985].

One week before starting the experiments, the animals were allowed to adapt to the ambient conditions. Preoperatively, anesthetic ketamine HCl (Ketalar®, Pfizer, Istanbul, Turkey) 40 mg/kg and xylazine (Rompun®, Bayer, Istanbul, Turkey) 5 mg/kg combination was administered intramuscularly. If required, during the experiment, administration of one additional dose of ketamine HCl was planned. During the procedure, anesthesia was delivered to maintain spontaneous respiration of the rats. The rats were lied down in the supine position on the heated table and under the heated lamp. Venous entry site was opened on the tail vein. After entry sites on the skin of all rats were aseptically prepared, midline laparotomy incision was made starting immediately below xyphoid and extending up to 0.5 cm above the pubis. After laparotomy, the intestines of the rats were wrapped into wet sterile gauze, and deviated to the upper side. During the experiment, for the purpose of fluid resuscitation 10 mL/kg 0.9% NaCl was given through the tail vein (Perfusor Compact, B. Braun®, Melsungen, Germany). Atraumatic micro vascular clamps were placed on bilateral renal arteries (Nova clip® 12 mm Angle, Plymouth, USA). Following clamping, disappearance of arterial pulsation and blanching the kidney color indicated renal ischemia, and reperfusion defined as the emergence of arterial pulsation and changing the kidney color to red again after removal of the clamp. After clamping, intestines were put in back, nearly 5 mL warm serum physiological solution was sprayed into the peritoneal cavity. To prevent fluid loss, laparotomy incision was approximated with three separate 4/0 silk sutures. After 45 min, clamps were removed and laparotomy incision was sutured with continuous 3/0 polypropylene sutures. Twenty-four hours after the first surgical intervention, with

Table 1. TNF-α scores for lung sections in all groups

	Lung TNF-α				
	(-)	(1+)	(2+)	Mean±SD	*p*
Control	4	2	1	0.8±0.6	
I/R	0	1	6	1.8±0.3	
I/R+cilostazol	3	4	0	0.5±0.5	<0.05
I/R+rosuvastatin	1	4	2	1.1±0.6	
I/R+cilostazol+rosuvastatin	1	4	2	1.1±0.6	

TNF-α: Tumor necrosis factor-alpha; SD: Standard deviation; I/R: Ischemia/reperfusion.

the same anesthetic protocol, laparotomy and median sternotomy were performed. Lungs and bilateral kidneys were extracted.

In the control group, no drug study medication was administered to the rats during preoperative period. Renal arteries were explored via laparotomy and renal arteries were not clamped after exploration. Laparotomy incision was sutured. Twenty four hours after the operation, organs were extracted and the rats were sacrificed.

In the I/R group, no drug study medication was administered to the rats during preoperative period. Renal arteries were clamped. Forty-five min after the clamping period, clamps were released and laparotomy incision was sutured. Twenty-four hours after the operation, organs were extracted and the rats were sacrificed.

Starting three days before the surgical intervention, daily cilostazol dose of 20 mg/kg (Cilostazol, Otsuka Pharmaceutical Co., Tokushima, Japan), rosuvastatin 10 mg/kg (Crestor, Astra Zeneca, IPR Pharmaceuticals Inc., Porto Rico), and cilostazol 20 mg/kg+rosuvastatin 10 mg/kg were given with gastric gavage at the same time each day to the

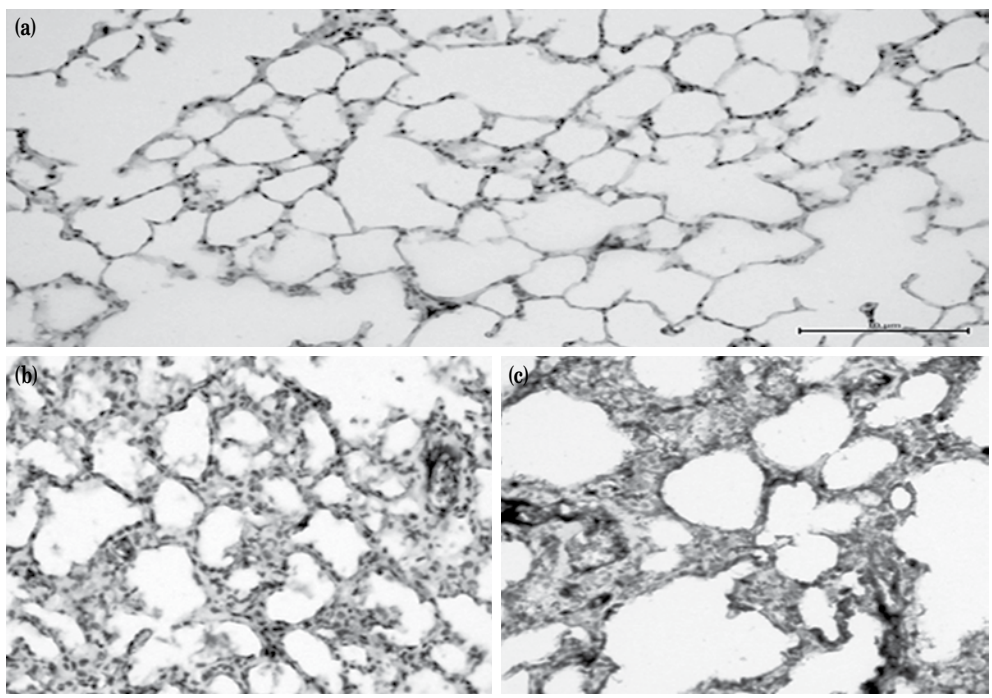

Figure 1. Lung cross sections; **(a)** Control group; TNF-α negative cytoplasmic staining, **(b)** I/R injury group with TNF-α immunoreactivity; intense cytoplasmic staining of TNF-α, **(c)** I/R injury group with HIF-1α immunoreactivity; 76-100% staining cytoplasmic and nuclear staining of HIF-1α (×200). TNF-α: Tumor necrosis factor-alpha; I/R: Ischemia/reperfusison; HIF-1α: Hypoxia-induced factor-1α.

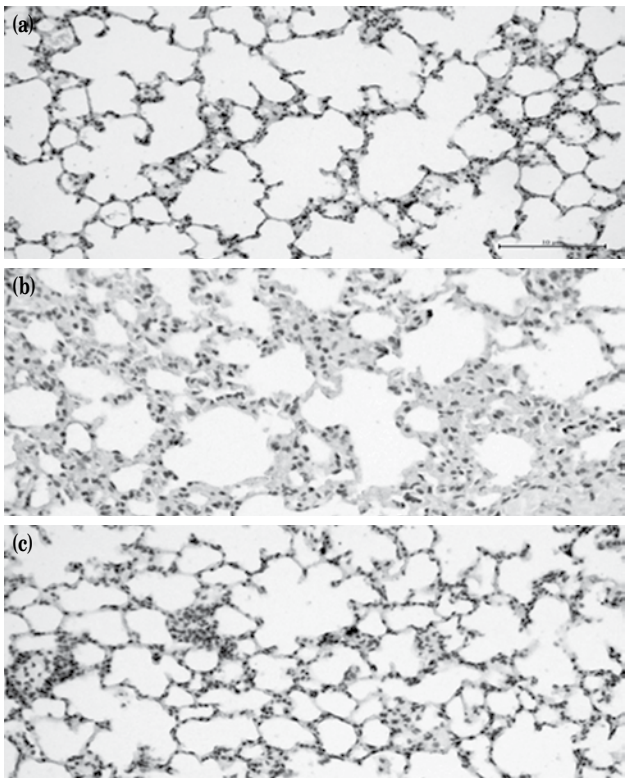

Figure 2. Lung cross sections; **(a)** TNF-α immunoreactivity in cilostazol group with no cytoplasmic staining, **(b)** TNF-α immunoreactivity in rosuvastatin group with no cytoplasmic staining, **(c)** TNF-α immunoreactivity in cilostazol+rosuvastatin group with no cytoplasmic staining (×200). TNF-α: Tumor necrosis factor-alpha.

I/R+cilostazol group, I/R+rosuvastatin group, and I/R+cilostazol+rosuvastatin group, respectively. On the fourth day, the first surgical intervention was performed. Renal arteries were occluded, and after 45 min of renal ischemia, clamps were removed. Abdominal layers were re-approximated. Twenty-four hours after the operation, organs were extracted and the rats were sacrificed.

Organs were stored in 10% formaldehyde solution until immunohistochemical examination was performed. A pathologist blinded to the study performed histopathological examinations using a light microscope (Olympus BX51, Olympus Optical Co., Ltd., Shinjuku, Tokyo, Japan).

Tumor necrosis factor-alpha (TNF-α; [4E1]: sc-130349. Santa Cruz Biotechnology, Inc., Santa Cruz, California, USA) and hypoxia-induced factor-1α (HIF-1α; [H1alpha 67]: sc-53546. Santa Cruz Biotechnology, Inc., Santa Cruz, California, USA) antibodies were used for immunohistochemical examinations of the lung. Density and intensity of dye uptake of the TNF-α antibody was evaluated as described by Khandoga et al.[6] TNF-α was evaluated as no staining (-), slight staining (+) and intense staining (++). Immunohistochemical findings according to the groups were calculated as 0 points for no staining (-), 1 point for slight staining (+) and 2 points for intense staining (++). HIF-1α was evaluated as (+) for 1-25% staining, (++) for 26-50% staining, (+++) for 51-75% staining and (+++) for 76-100% staining and they were given degrees as 0, 1, 2, 3 and 4, respectively. Cytoplasmic staining for TNF-α and, nuclear and cytoplasmic staining for HIF-1α was accepted as positive.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median, frequency, and percentage values. The Kruskal-Wallis and Mann-Whitney U tests were used to analyze significant differences among the groups. A p value of <0.05 was considered statistically significant.

Table 2. HIF-1α scores for lung sections in all groups

	Lung HIF-1α					
	(1+)	(2+)	(3+)	(4+)	Mean±SD	p
Control	5	2	0	0	1.2±0.4	
I/R	0	4	2	1	2.5±0.7	
I/R+cilostazol	7	0	0	0	1.0±0.0	<0.05
I/R+rosuvastatin	6	1	0	0	1.1±0.3	
I/R+cilostazol+rosuvastatin	7	0	0	0	1.0±0.0	

HIF-1α: Hypoxia induced factor-1 alpha; SD: Standard deviation; I/R: Ischemia/reperfusion.

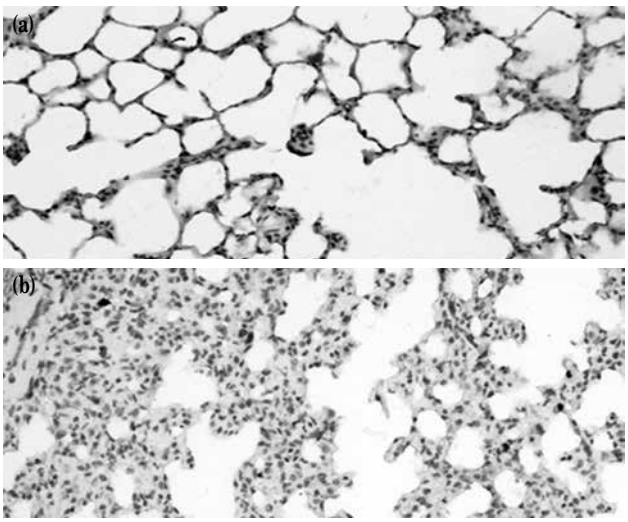

Figure 3. Lung cross sections; **(a)** HIF-1α immunoreactivity in rosuvastatin group; 1-25% nuclear and cytoplasmic staining **(b)** HIF-1α immunoreactivity in cilostazol + rosuvastatin group; 1-25% nuclear and cytoplasmic staining (×200). HIF-1α: Hypoxia-induced factor-1α.

RESULTS

TNF-α Immunoreactivity

The immunohistochemical evaluation of lung cross-sections revealed that TNF-α immunoreactivities in I/R+cilostazol, I/R+rosuvastatin, and I/R+cilostazol+rosuvastatin groups were found to be decreased significantly compared to I/R group ($p<0.05$). Lung TNF-α immunoreactivities in I/R+rosuvastatin and I/R+cilostazol+rosuvastatin groups was found to be increased significantly, compared to control group ($p<0.05$), while TNF-α immunoreactivity of I/R+cilostazol group was found similar, compared to control group ($p>0.05$). TNF-immunoreactivity was not significantly different between I/R+rosuvastatin and I/R+cilostazol+rosuvastatin groups ($p>0.05$) (Table 1 and Figure 1, 2).

HIF-1α Immunoreactivity

The immunohistochemical evaluation of lung cross-sections revealed that HIF-1α immunoreactivities in I/R+cilostazol, I/R+rosuvastatin, and I/R+cilostazol+rosuvastatin groups were found to be decreased significantly compared to I/R group ($p<0.05$). HIF-1α immunoreactivites among I/R+cilostazol, I/R+rosuvastatin and I/R+cilostazol+rosuvastatin groups were found similar compared to control group ($p>0.05$). HIF-1α immunoreactivity was not significantly different among I/R+cilostazol, I/R+rosuvastatin, and I/R+cilostazol+rosuvastatin groups ($p>0.05$) (Table 2 and Figure 3).

DISCUSSION

Ischemia/reperfusion injury is the major cause of the inflammatory activation after cardiovascular practices. Kidney, lung, and heart damage after I/R injury affect patients' postoperative morbidity and mortality. When reperfusion starts after the ischemic period of the extremities or organs, inflammation activates and inflammatory mediators are released to circulation. Of note, TNF-α, interleukins, HIF-1α and oxygen radicals are the most important triggers for inflammation.[7] After releasing of these mediators leukocytes activate and they infiltrate to target organs' endothelium. Oxygen radicals enhance adhesion of leukocytes. Endothelial nitric oxide decreases I/R-induced lung injury.[8] These mediators affect all organs and they cause deficiency in kidney, lung, and heart. In this study, we used TNF-α and HIF-1α as a determinant of inflammation in the lung and we showed the anti-inflammatory effects of cilostazol and rosuvastatin with these indicators.

Cilostazol is the most used drug for peripheral vascular disease today and it has beneficial effects for this disease. Rosuvastatin is an anti-hyperlipidemic drug and it protects endothelial continuity as decreasing serum lipid level. However, today, we see that there are many of study in the literature about protective effects of cilostazol and rosuvastatin against I/R injury-induced inflammation. In a study by Matsuo et al.,[8] the protective effect of rosuvastatin in the lung I/R injury after left pulmonary artery occlusion was investigated in rats with pulmonary hypertension. The authors found decreased macrophage infiltration in the lung. Endothelial nitric oxide synthase decrease was also blocked in the rosuvastatin group. In another study by Ferreira et al.,[9] an experimental lung inflammation model was designed using cigarette smoke and they investigated lung inflammation without I/R injury and they found that all of the statins have anti-inflammatory effects. However, rosuvastatin demonstrated the highest anti-inflammatory effects and simvastatin showed the highest antioxidant effects. In another study, protective effects of simvastatin was investigated in an ischemic lung experimental model and it was showed that simvastatin also had the ability of endothelial nitric oxide synthase modulation and it had beneficial effects on lung ischemia.[10] In a study by Awad and El Sharif,[11] a hepatic I/R model was designed and it was aimed to measure immunomodulatory effects of rosuvastatin in liver,

lung, kidney, intestine, and heart tissues. They showed that rosuvastatin pretreatment appears to protect these organs after hepatic I/R injury through the reduction of TNF-α and IL-6. In the light of these studies, we can conclude that rosuvastatin have anti-inflammatory effects. We may benefit from its anti-inflammatory and antioxidant effect in many of inflammatory-mediated disease. Therefore, we aimed to examine its effect in kidney I/R injury-induced lung injury model.

Cilostazol, which is a type 3 phosphodiesterase inhibitor, has anti-platelet and anti-thromboembolic effects. It also inhibits smooth muscle proliferation. In an experimental study by Chang et al.,[12] pulmonary blood flow was improved and pulmonary arterial pressure was reduced in rats with pulmonary hypertension. They showed increased endothelial nitric oxide synthase expression in lung as being previously mentioned in rosuvastatin studies. The beneficial effect of cilostazol decreasing the pulmonary arterial pressure is supported with many studies.[13] Ragap et al.[14] also studied about renoprotective effect of cilostazol. They designed a renal I/R model, they showed that cilostazol decreased inflammatory mediator activation after renal I/R, and cilostazol alleviated incidents associated with acute renal injury. In our previous study, we also showed similar results with this study and we showed beneficial effect of cilostazol on kidney I/R injury.[5] Gokce et al.[15] designed a study to evaluate the effects of cilostazol and diltiazem to counter the nephrotoxicity-induced by the calcineurin inhibitor cyclosporine. They showed cilostazol and diltiazem were effective to decrease renal I/R injury. In another experimental study investigating the protective effects of cilostazol and levosimendan on lung injury after lower extremity ischemia, Onem et al.[16] performed 60 min abdominal aortic cross-clamping and evaluated malondialdehyde levels, superoxide dismutase activity, and glutathione levels in the lung tissues. The authors showed that cilostazol and levosimendan restored malondialdehyde levels, superoxide dismutase activity, glutathione levels, and lung injury scores. They concluded that pretreatment with cilostazol and levosimendan may be useful to prevent lower limb-induced lung reperfusion injury. Several studies in the literature show that cilostazol also has anti-inflammatory and antioxidant effects as much as rosuvastatin. Therefore, we hypothesized that combination of these drugs may be more beneficial preventing remote lung injury.

There are not many studies in the literature which investigate the protective effects of cilostazol and rosuvastatin on lungs after kidney I/R injury. In this study, we designed an acute kidney injury model and we evaluated reperfusion damage of acute kidney injury and inflammatory effects of kidney injury during 24 hours on lungs. In our previous study, we showed 45 min kidney ischemia and remote myocardial injury. We showed its inflammatory damage in tissues using TNF-α and HIF-1α immunoreactivity. We also found that cilostazol and rosuvastatin had beneficial effects on direct kidney ischemia and kidney ischemia-induced myocardial injury. The protective effect of rosuvastation was lower, compared to cilostazol or combined therapy.[5] In this study, we continued the same medication in the same animal group and we examined the beneficial effects of these drugs on lungs after kidney I/R injury. Based on our results, lung tissue examinations showed that HIF-1α immunoreactivity was decreased significantly in cilostazol, rosuvastatin, and combination group. The results were almost similar to the control group. However, rosuvastatin group and combination treatment group showed higher damage scores than the control group in TNF-α immunoreactivity sections. However, all of the results were significantly lower compared to I/R group. We believe that cilostazol and rosuvastatin seems to be more effective in lungs than in myocardium, compared to our previous study.

In conclusion, our study results suggest that preoperative use of cilostazol and rosuvastatin have beneficial effects for the prevention of acute kidney injury-induced reperfusion injury in lungs and combined use of these drugs does not decrease beneficial effects of them for lungs.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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