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Original Article / Özgün Makale

Rosuvastatin pretreatment does not attenuate microalbuminuria after coronary artery bypass grafting

Rosuvastatin ön tedavisi koroner arter baypas greftleme sonrasında mikroalbuminüriyi azaltmaz

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Background: This study aims to evaluate whether rosuvastatin attenuates microalbuminuria following coronary artery bypass grafting (CABG) with a cardiopulmonary bypass (CPB).

Methods: This prospective study was performed in 40 patients (37 males, 3 females; mean age 59.0±10.1 years; range 48 to 78 years) who were scheduled for isolated CABG. The patients were divided into two groups including control group (n=20) and rosuvastatin group (n=20) which received rosuvastatin 20 mg/day seven day (20 mg/day) before elective CABG. Microalbuminuria was measured after the insertion of the urinary catheter, before CPB, after the termination of CPB, and at the sixth and 24th hours in the intensive care unit using a spot urine sample. Serum C-reactive protein was measured before the induction of anesthesia and at the sixth and 24th hours in the intensive care unit using blood samples.

Results: The demographic data and preoperative characteristics of the patients were similar. There were no significant differences in the CPB, cross-clamp and surgery time, inotropic support, extubation times, and time to discharge from hospital between the two groups. The urinary albumin/creatinine ratio increased in both groups, compared to the baseline measurement and reached a maximum level at the end of CPB ($p<0.05$). Albumin/creatinine ratio measured at the sixth hour in the intensive care unit was significantly higher in the rosuvastatin group (0.69 vs. 2.10, $p=0.002$). Serum C-reactive protein increased at 24 hour postoperatively in both groups.

Conclusion: Rosuvastatin pretreatment does not attenuate microalbuminuria and the inflammatory response after CABG surgery.

Keywords: Coronary artery bypass grafting surgery; microalbuminuria; rosuvastatin; systemic inflammatory response.

Amaç: Bu çalışmada rosuvastatinin, kardiyopulmoner baypas (KPB) eşliğinde yapılan koroner arter baypas greftleme (KABG) sonrasında mikroalbuminüriyi azaltıp azaltmadığı araştırıldı.

Çalışma planı: Bu prospektif çalışmaya izole KABG yapılan toplam 40 hasta (37 erkek, 3 kadın; ort. yaş 59.0±10.1 yıl; dağılım 48-78 yıl) alındı. Hastalar kontrol grubu (n=20) ve elektif KABG'den yedi gün önce 20 mg/gün rosuvastatin kullanmış hastalardan oluşan rosuvastatin grubu (n=20) olarak ikiye ayrıldı. Tüm hastalardan mikroalbuminüri idrar sondası takıldığında, KPB'nin başlangıcından önce, KPB'nin sonlandırıldığı anda ve yoğun bakım ünitesinde altıncı ve 24. saatlerde spot idrar örneği ile ölçüldü. Serum C-reaktif protein ise anestezi indüksiyonundan önce ve yoğun bakım ünitesinde altıncı ve 24. saatte kan örneği ile ölçüldü.

Bulgular: Hastaların demografik verileri ve ameliyat öncesi özellikleri benzerdi. Gruplar arasında KPB, kros klemp ve ameliyat süreleri, inotrop desteği, ekstübasyon süreleri ve hastaneden taburculuk süreleri arasında anlamlı fark bulunmadı. Üriner albümin/kreatinin oranları her iki grupta başlangıç ölçümüne kıyasla artmıştı ve KPB sonunda maksimum düzeye ulaştı ($p<0.05$). Yoğun bakımda altıncı saatte ölçülen albümin/kreatinin oranı, rosuvastatin grubunda anlamlı düzeyde yüksekti (0.69'a kıyasla 2.10, $p=0.002$). Serum C-reaktif protein her iki grupta da cerrahi sonrası 24. saatte artış gösterdi.

Sonuç: Rosuvastatin ön tedavisi, KABG sonrasında mikroalbüminüriyi ve inflamatuvar yanıtı azaltmaz.

Anahtar sözcükler: Koroner arter baypas greftleme cerrahisi; mikroalbuminuri; rosuvastatin; sistemik inflamatuar yanıt.

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Despite improvements in perioperative care and surgical techniques, coronary artery bypass graft (CABG) surgery is often followed by a systemic inflammatory response.[1,2] A very early feature of this inflammation is an increase in capillary permeability to plasma proteins that occurs within a few minutes of injury.[3]

Microalbuminuria reflects these rapid changes in systemic capillary permeability and is defined as a persistent increase in the urinary excretion of albumin, ranging from 30 to 300 mg/d or from 20 to 200 mg/L. The Albumin-to-Creatinine Ratio (ACR), which reflects the microalbuminuria, minimizes the effect of variations in urine flow and can be measured from a single specimen. Microalbuminuria may appear within a few hours following the beginning of acute conditions such as trauma, surgery,[4] and ischemia-reperfusion (IR) injury.[5] Similarly, cardiopulmonary bypass (CPB) activates the inflammatory cascade, leading to increases in capillary permeability and causing microalbuminuria.

Experimental and clinical evidence indicates that some of the cholesterol-independent or pleiotropic effects of statins involve the improvement and restoration of endothelial function, the enhanced stability of atherosclerotic plaques, the attenuation of thrombogenesis, and decreased oxidative stress (OS) and inflammation.[6,7] In addition, statin pretreatment has been demonstrated to reduce the inflammatory response,[8] myocardial damage, morbidity, and mortality after CABG surgery.[9,10]

The aim of this study was to investigate whether rosuvastatin pretreatment (20 mg/d) attenuates microalbuminuria as a marker of increased capillary permeability following CABG surgery performed via CPB.

PATIENTS AND METHODS

We performed a prospective, randomized, and placebo-controlled study on 40 patients (37 males, 3 females; mean age 59.0±10.1 years; range 48 to 78 years) who underwent elective isolated CABG surgery between October 2010 and June 2011 and also satisfied the study selection criteria. The institutional ethics committee approved our study, and we obtained the informed consent of each patient for their participation. We excluded those with chronic diseases [e.g., diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD)], renal (increased creatinine and blood urea nitrogen levels) or hepatic impairment (increased alanine aminotransferase and aspartate aminotransferase levels), poor cardiac function [ejection fraction (EF) <35%), a history of myocardial infarction (<3 months), or a history of inflammatory or immunomodulatory diseases. Furthermore, patients who had undergone previous heart surgery, those who had received previous (60d) therapy with steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs) or previous (30 days) treatment with statins, and those with a contraindication to statin treatment were also not included. The patients were randomly placed in either the group treated with rosuvastatin (RSV) (n=20) or the control group (n=20). Those in the RSV group received 20 mg/day seven days prior to their surgery. In addition, none of the patients had microalbuminuria when they were assessed preoperatively.

A standard anesthetic technique was used which consisted of weight-related doses of fentanyl, midazolam, and vecuronium bromide. Following premedication, venous and radial artery catheters were inserted along with a urinary catheter after the induction of anesthesia. Next, CPB was established using a Stöckert S5 modular heart-lung machine (SORIN GROUP Deutschland GmbH, München, Germany) and the Affinity® NT oxygenation system (Medtronic, Inc., Minneapolis, MN, USA). Mild hypothermia (33 °C to 34 °C) was also applied with nonpulsatile flows of 2.4 L/min/m^2. The circuit was primed with 1500 ml of Ringer's lactate, 150 ml of 20% mannitol, and 5000U heparin. All of the operations were performed through a median sternotomy, after which CPB via the cannulation of the ascending aorta and right atrium was instituted while maintaining a mean systemic pressure of between 50 and 70 mmHg. Cardiac arrest was then induced by the administration of intermittent cold blood cardioplegia (4:1 dilution, blood: cardioplegia) through the antegrade and retrograde routes. After completing the last distal anastomosis, warm blood cardioplegia was infused before declamping the aorta. The left internal thoracic artery (LITA) was used in all cases to revascularize the left anterior descending artery (LADA). At the end of the surgery, the patients were transferred to the intensive care unit (ICU). The standard mode of mechanical ventilation was used on all of the patients, and they were ventilated with volume control ventilation and a tidal volume of 10 ml/kg with 5 cm H_2O of positive end-expiratory pressure. The patients were extubated when they were hemodynamically stable, fully rewarmed and awake. None had surgical bleeding and all had optimal blood gas levels. Additionally, no steroids were administered during the procedure.

Urine samples were collected at the following time points: after the insertion of the urinary catheter, before

Table 1. Patient characteristics and operative data

Parameters	Control group			Rosuvastatin group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age			57.8±9.5			60.1±10.62	0.47
Number of females	–	–		3	15		0.23
Body mass index			27.6±2.9			26.6±4.80	0.43
Current smokers	5	25		6	30		0.90
Ejection fraction			54.6±7.1			56±6.41	0.51
Left main coronary artery	–	–		–	–		–
Blood urea nitrogen (mg/dl)			17.7±4.6			18.2±5.1	0.74
Creatinine (mg/dl)			1.3±0.6			0.8±0.1	0.24
Total cholesterol (mg/dl)			193.9±49.1			186.3±42.5	0.60
Low density lipoprotein (mg/dl)			124.2±49.7			121.4±37.6	0.84
High density lipoprotein (mg/dl)			34.7±6.2			35±7.2	0.88
Cardiopulmonary bypass time (minutes)			75.4±19.6			76.3±20.7	0.88
Aortic cross-clamp time (minutes)			65.4±19.6			63.4±20.7	0.71
Number of distal anastomoses			2.5±0.5			2.5±0.6	1

SD: Standard deviation.

CPB, right after the termination of CPB, six hours after their arrival in the ICU, and at the postoperative 24th hour. The samples were then stored at -20 °C and analyzed after they had all been collected. The urinary albumin concentrations were measured by a nephelometer (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) while the urinary creatinine concentrations were measured using a spectrophotometer (Abbott Laboratories, Abbott Park, IL, USA).

The serum C-reactive protein (CRP) concentration, a common marker for inflammation and tissue damage,[11] was determined from blood samples taken via the radial artery catheter before the induction of anesthesia, six hours after their arrival in the ICU, and at the 24th hour in the ICU. In addition, the C-reactive protein (CRP) concentrations were measured utilizing a nephelometer (Radim SpA, Pomezia, Italy).

Statistical analysis

The categorical data was expressed in absolute numbers (percentages), and median and minimum and maximum values were used for continuous variables. A comparison between the continuous variables in the two groups was performed using the Mann-Whitney U test since the data was not normally distributed. Furthermore, the differences between the measurements within the groups were determined using the Friedman test, and multiple comparisons were made using the Iman-Conover method. Moreover, the categorical variables were analyzed with either a Chi-square test or Fisher's exact test, and a p value of less than 0.05 was considered to be statistically significant.

RESULTS

Table 1 shows the patient characteristics and operative data. The two groups were homogeneous according to age, gender, and echocardiographic features, and the mean number of distal anastomoses and CPB along with the aortic cross-clamp times were all similar. Furthermore, all of the operations proceeded uneventfully.

The postoperative outcomes are presented in Table 2. We found no significant differences between the two groups regarding ventilation time or length of ICU or hospital stays. Postoperative atrial fibrillation (AF) occurred in five patients in the RSV group compared with three patients in the control group (p=0.69), but amiodarone infusion restored sinus rhythm in all of the cases.

The urinary ACR levels are provided in Table 3, with a maximum level being reached at the end of CPB in both the control (ACR1=1.16 vs. ACR3=23.90; p<0.05) and RSV groups (ACR1=1.22 vs. ACR3=19.00; p<0.05) (Figure 1 and Table 3), but there were no statistically significant differences between the groups. However, at the sixth hour, the ACR4 was higher in the RSV group, and this was statistically significant compared with the control group (0.69 vs. 2.10, p=0.002). In addition, the serum CRP increased at the postoperative 24th hour in both groups but no statistically significant differences were seen (p>0.05) (Figure 2).

DISCUSSION

Our findings indicated that preoperative rosuvastatin therapy is not associated with improvement in

Table 2. Postoperative outcomes

Parameters	Control group			Rosuvastatin group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Ventilation time (hours)			6.0±1.7			6.3±1.8	0.59
Postoperative bleeding (ml/24 hrs)			432.5±179.4			502.5±315.2	0.39
Revision for bleeding	–	–		–	–		–
Need for inotropic support	3	15		3	15		0.90
Atrial fibrillation	3	15		5	25		0.69
Blood transfusion (units)			0.4±0.6			0.3±0.6	0.78
Intensive care unit stay (days)			2.3±0.6			2.2±0.4	0.52
Stroke	–	–		–	–		–
Early mortality	–	–		–	–		–
Myocardial infarction	–	–		–	–		–
Hospital stay (days)			7.0±0.2			7.4±1.0	0.10

SD: Standard deviation.

microalbuminuria and increased capillary permeability in patients who undergo CABG surgery.

Studies have demonstrated that statins are associated with a reduction in the incidence of a variety of deleterious outcomes, including myocardial infarction, low cardiac output syndrome, stroke, AF, renal failure, infection, prolonged hospital stays, delirium, and mortality,[8-10] and the responsible mechanism is related to both lipid-lowering and pleiotropic effects, such as those that are in an antithrombotic, anti-inflammatory, antioxidant, or plaque- and endothelium-stabilizing state. Laufs et al.[12] reported that statins inhibit Rho function and upregulate endothelial nitric oxide synthase (eNOS) while van Nieuw Amerongen et al.[13] demonstrated improvement in the disturbed endothelial barrier function in patients treated with simvastatin treatment.

In this study, the ACRs measured before and after CPB were lower in the RSV group than the control group; however, this difference was not statistically significant. On the other hand, the ACR at the sixth hour in the ICU was significantly higher in the RSV group.

In contrast to previous reports which found that experimental hyperpermeability can be ameliorated by the indirect inhibition of RhoA/Rho kinase signaling with statins,[14,15] our findings indicated that statins do not ameliorate increased permeability. Two

Table 3. Urinary albumin/creatinine ratio

	Median	Minimum	Maximum	*p*
Albumin/creatinine ratio 1				
Control	1.16	0.30	27.71	0.745
Rosuvastatin	1.22	0.51	17.51	
Albumin/creatinine ratio 2				
Control	20.13	2.85	101.00	0.374
Rosuvastatin	17.68	6.24	22.01	
Albumin/creatinine ratio 3				
Control	23.90	1.55	588.24	0.607
Rosuvastatin	19.00	0.78	155.29	
Albumin/creatinine ratio 4				
Control	0.69	0.35	3.30	0.002*
Rosuvastatin	2.10	0.36	21.00	
Albumin/creatinine ratio 5				
Control	1.08	0.43	6.92	0.123
Rosuvastatin	1.66	0.63	5.42	

The urinary albumin/creatinine ratio was measured at the following time points: after the insertion of the urinary catheter, before cardiopulmonary bypass, just after the termination of cardiopulmonary bypass, six hours after arriving in the intensive care unit, and at the postoperative 24th hour; * $p<0.05$.

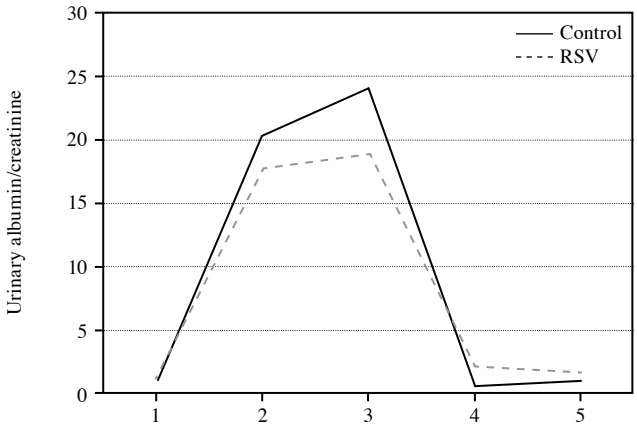

Figure 1. This shows the urinary albumin/creatinine ratio levels at the following time points: 1) after the insertion of the urinary catheter, 2) before cardiopulmonary bypass, 3) just after the termination of cardiopulmonary bypass, 4) six hours after arriving in the intensive care unit, and 5) at the postoperative 24th hour. RSV: Rosuvastatin.

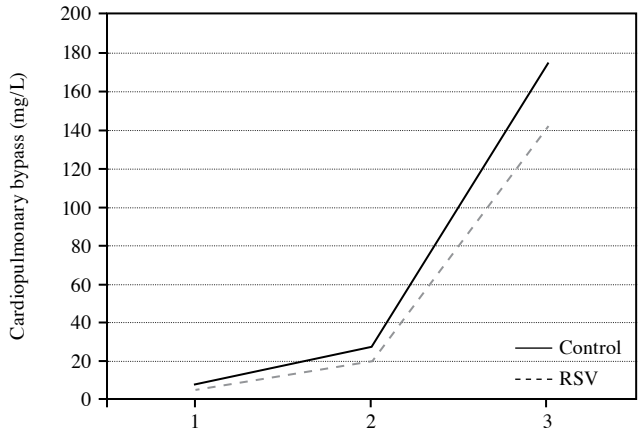

Figure 2. This shows the C-reactive protein levels at the following time points: 1) before the induction of anesthesia, 2) at the sixth hour in the intensive care unit, 3) at the postoperative 24th hour. RSV: Rosuvastatin.

explanations could account for our findings. First, high doses of statins were used in the experimental studies, and secondly, the withdrawal of statin therapy on the day of surgery might have resulted in suboptimal circulating statin levels, causing the downregulation of endothelial NO production.[16] Vecchione and Brandes[17] showed that endothelium-dependent relaxation did not change during the first four days after statin withdrawal in mice, and Laufs et al.[12] reported that the withdrawal of statins in mice resulted in a transient increase in Rho activity and a suppression of eNOS production no earlier than two days afterwards. This data suggests that the effects of statin could have lasted long enough to influence the postoperative permeability in our study. Similar to our findings, van de Visse et al.[18] found that regular doses of statins do not protect against pulmonary vascular hyperpermeability caused by surgery-associated IR.

Preoperative statin therapy was associated with a decrease in the incidence of postoperative AF in the Atorvastatin for Reduction of Myocardial Dysrhythmia after Cardiac Surgery (ARMYDA-3) study.[19] Furthermore, Mannacio et al.[20] reported that rosuvastatin pretreatment (20 mg/d) for seven days reduced the incidence of AF after CABG surgery as a result of the statins' anti-inflammatory effects and protective activity against tissue injury. In contrast, our study showed a insignificant increase in the incidence of postoperative AF with preoperative statin therapy in the patients who underwent CABG surgery.

This study also confirmed that CPB is associated with a significant inflammatory response, as evidenced by the increased CRP values, but even with treatment, the RSV group showed no improvement in this area.

A limitation of this study was that other inflammatory biomarkers, such as interleukin-6 and tumor necrosis factor alpha, were not measured for a comparison. In addition, the number of the patients used in the study might have been too small.

In conclusion, our findings suggest that 20 mg/day rosuvastatin pretreatment for seven days does not attenuate vascular leaks or hyperpermeability after CABG surgery.

Declaration of conflicting interests

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