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Araştırma

Remote Preconditioning Might Protect the Kidney in Heart Surgery

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ABSTRACT

Objective: *There are conflicting results about renoprotective effects of remote ischemic preconditioning (RIPC) reported in previous studies. This study is designed to investigate the effects of this application on renal function by means of certain deliberate biomarkers during the early postoperative period in patients undergoing coronary artery bypass graft (CABG) surgery.*

Material and Methods: *This prospective, randomized, and blinded study was performed in patients who underwent isolated CABG surgery together with cardiopulmonary bypass (CPB) after eliminating factors that may confound biomarkers that indicate renal ischemia-reperfusion injury. The authors randomly assigned patients to RIPC to the left lower extremity using an inflated (study group) or deflated (control group). blood pressure cuff. Renal functions were analyzed by measuring cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and creatinine levels at 3 different time points namely 1 hour (T1) after CPB and 6 hours (T2) after skin closure, and 24 hours postoperatively (T3).*

Results: *There were no differences between the two groups in terms of demographic values and the hemodynamic parameters. Plasma cystatin C and creatinin levels were significantly higher in the control group than those of the study group at all time points. Plasma NGAL levels were higher in the control group than in the study group at two time points, p=0,001 for time; p=0,243 for group respectively.*

Conclusion: *In low risk patients with on- pump CABG surgery, RIPC seems to protect renal functions. Further studies with different risk groups should also be planned to determine whether this procedure is useful in cardiac surgery patients.*

Keywords: *remote preconditioning, renal injury, coronary surgery*

ÖZ

Uzak Ön Koşullanma Kalp Cerrahisinde Böbreği Koruyabilir

Amaç: *Uzak-iskemik ön koşullanmanın böbrek üzerine olan koruyucu etkileri hakkında birbiriyle çelişen pek çok çalışma bulunduğu için bu uygulamanın koroner arter baypas (CABG) cerrahisi geçiren hastalarda erken postoperatif dönemde böbrek koruyucu etkisi olup olmadığını belirli biyobelirteçler aracılığıyla araştırmak amacıyla bu çalışma planlandı.*

Gereç ve Yöntem: *Prospektif, randomize, kör çalışma; kardiyopulmoner baypas kullanılarak koroner arter baypas cerrahisi yapılan hastalarda (iskemi-reperfüzyona bağlı böbrek hasarını gösteren biyobelirteçlerde karışıklığa neden olabilecek faktörler elimine edildikten sonra) yapıldı. Hastalar randomize olarak pressure-cuff şişirilerek uzak-iskemik ön koşullanma yapılan (çalışma grubu) ve yapılmayan (kontrol grubu) 2 gruba ayrılmıştır. Böbrek fonksiyonları için 2 farklı zamanda; (T1: kardiyopulmoner baypastan 1 saat sonra, T2: cilt kapandıktan 6 saat sonra ve T3: postoperatif 24. saatte); sistatin C, nötrofil gelatinaz ilişkili lipokalin (NGAL) ve kreatinin düzeyleri incelenmiştir.*

Bulgular: *Her 2 grup arasında demografik veriler ile hemodinamik parametreler arasında istatistiksel olarak anlamlı bir fark bulunamadı. Plazma sistatin C ve kreatinin değerleri bütün örnekleme zamanlarında kontrol grubunda çalışma grubuna göre anlamlı olarak farklı bulundu. Plazma NGAL düzeyleri kontrol grubunda çalışma grubuna göre iki örneklemede p=0.001 zaman, p=0.243 grup değerleri bulundu.*

Sonuç: *Düşük riskli hastalarda kardiyopulmoner baypaslı CABG cerrahisi öncesi uygulanan uzak-iskemik ön koşullanma yönteminin böbrek fonksiyonlarını koruduğu görülmektedir. Bu yöntemin kalp cerrahisi hastalarında yararını gösterebilmek için farklı risk gruplarındaki hastalar için ileri çalışmalar planlanmalıdır.*

Anahtar kelimeler: *uzak ön koşullanma, böbrek hasarı, koroner cerrahi*

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INTRODUCTION

Impairment of renal function is a widespread and dangerous complication of cardiac surgery with cardiopulmonary bypass (CPB). Renal ischemia could occur during CPB as a result of complex interactions among the effects of blood viscosity changes due to hemodilution and hypothermia, the absence of blood flow pulsatility and hypotension [1,2,3]. In order to provide some protection from these destructive changes, application of Remote Ischemic PreConditioning (RIPC) has been introduced into the clinical practice by some investigators. The application of transient, and short periods of ischemia in a distant organ or extremity are considered to trigger pathways that allow protection in the target organs against a subsequent, more prolonged ischemia due to CPB used in cardiac surgery [4,5,6,7].

The procedure for RIPC is simple and has low adverse effect profile which renders it attractive for most clinical applications. There are conflicting results about renoprotective effects of RIPC in the previous studies [6,8,9,10]. Therefore we planned to examine the effects of RIPC on renal function by means of certain deliberate biomarkers in the early postoperative period in patients with cardiopulmonary bypass applied during coronary artery surgery [11,12,13].

Some of these studies were not prospective and patient population was not homogenous contrary to our study. Rise in creatinine levels is delayed after an acute injury like CPB. This complicates the condition, the diagnosis is overlooked, and therapeutic measures of renal injury are neglegted [14]. Thus we analyzed renal functions by measuring cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and also creatinine levels. These new markers are studied so the primary aim of the study was to demonstrate whether or not RIPC has any protective effect against renal injury in CABG surgery patients. We did not aim to include the patients in the category of Acute Kidney Injury (AKI). The secondary aim was to identify early renal injury in advance by using different and more sensitive kidney damage markers.

MATERIAL and METHODS

The study was started after obtaining approval of our Institutional Research Local Ethics Committee. The written informed consent from all patients were also obtained. This prospective, randomized, controlled and blinded study conformed to the Helsinki Declaration principles. The CABG surgery patients with normal preoperative renal function test results,and normal glomerular filtration rate (GFR) were investigated in this trial.

Patients were evaluated preoperatively to determine the presence of any one of the following exclusion criteria that were shown in Table 1 [15,16,17,18]. The determination of these criteria are important because some of them could interfere with preconditioning procedure.

Patients who met the inclusion criteria of the study were randomized into 2 groups - Group S (study group) that underwent or Group C (control group) that did not undergo RIPC with a lower extremity cuff. The patients, the surgical team, the intensive care unit (ICU) staff and biochemical analysts were blinded with respect to the study groups and the procedure applied.

Remote ischemic preconditioning protocol consisted of three 5 minute cycles of left lower extremity ischemia induced by a blood pressure cuff placed on the left lower extremity over the thigh region and inflated to 200 mmHg, with an intervening 5 minutes of reperfusion during which time the cuff was deflated. The cuff was placed on the left lower extremity because the saphenous vein was harvested from the right leg. The control patients had an uninflated cuff placed on the left lower extremity for 30 minutes. The remote ischemic preconditioning protocol was performed after anesthetic induction and before the beginning of the surgery.

Anesthetic management

All operations were electively performed in our clinic. The anesthetic management was also the same for all patients. All patients were anesthetized with fentanyl (3-5 μg/kg), and etomidate (0.1-0.2 mg kg^{-1}) for induction. Neuromuscular blockade was achieved by rocuronium bromide (0.6 mg kg^{-1}). Anesthesia was maintained using either a continuous intravenous infusion of fentanyl (30-50 μg kg^{-1}), and midazolam (2-3 mg h^{-1}).

Surgical Procedure

The surgical techniques were the same in all cases. All operations were performed by the same surgical team, anesthesiologist and perfusionist. The surgical procedure was performed through a median sternotomy incision with the patient under moderate hypothermia (30-32 °C). The same anesthetic and cardioplegic protocols were used in all patients. Myocardial protection was provided intermittently using tepid, high-potassium-blood antegrade cardioplegia (1,000 mL initially) that was repeated at every 20 minutes. CPB was setup using a membrane oxygenator and roller pump, keeping the arterial partial oxygen pressure between 150 and 250 mmHg. Heparin was administered (300 IU kg^{-1}) for initial anticoagulation before onset of cannulation and supplemented as required to maintain an activated coagulation time more than 400 seconds. This was neutralized by protamine sulfate after weaning from cardiopulmonary bypass. Average flow rate was 2.4 L min^{-1} m^{2-1}. Left internal mammary (thoracic) artery was used as a graft for the left anterior descending artery bypass in all patients, and the greater saphenous vein for the other coronary bypasses. Proximal anastomoses were completed on the beating heart using an partial aortic occlusion clamp. Propofol infusion was not preferred because of its known interaction with cytokines and its effects on inflammatory responses, and antioxidants [19,20].

Hemodynamic Measurements

Standard monitorization of left radial artery blood pressure was performed, and Swan-Ganz catheters via the right internal jugular vein were placed before anesthesia induction. Hemodynamic parameters such as heart rates, mean arterial pressures, central venous pressures, and pulmonary capillary wedge pressures were recorded before the operation (H0), after termination of CPB (H1), and 2, (H2) and 18 hours (H3) postoperatively per study protocol. Hemodynamic values like cardiac output, cardiac index, systemic vascular resistance index, and left ventricular stroke work index also were measured using thermodilution (Datascope-Ohmeda, NJ, USA). Total amounts of drainage and the number of blood products used (units) in the postoperative period were recorded and compared between groups. Duration of ventilation, inotropic agent requirement, length of ICU and hospital stay also were recorded and compared.

Sampling and Biochemical Analysis

All samples obtained and parameters measured were examined according to the following procedure: Repetitive arterial blood samples were collected for the analysis of cystatin C, NGAL and creatinine at 3 different time points namely just before the induction of anesthesia (T0), 1 hour (T1) after weaning from cardiopulmonary bypass and 6 (T2) and 24 hours after operation (T3). The blood samples collected were centrifuged immediately at 1,000 g for 15 minutes, and the serum samples were stored at -80°C until assays for biochemical markers were performed.

Cystatin C

Serum cystatin C concentration (normal value, 0.58-1.02 mg L^{-1}) was measured using immunoturbidimetric method using commercial reagents on analyzer (Cobas-C-501 Roche Diagnostics GMBH Mannheim, Germany).

NGAL

Serum NGAL concentration (normal value, 108-235 ng mL^{-1}) was measured using enzyme-linked immunosorbent assay method (ELISA) with commercial (Quantikine human Lipocalin-2/NGAL, R&D Systems Europe Ltd. Abington UK) reagents.

Creatinine

Serum creatinine concentration (normal value, 0.7-1.3 mg mL^{-1}) was measured using enzymatic colorimetric method with commercial reagents on analyzer (Advia 180, Siemens Health Diagnostics Inc. Newyork, USA).

Statistical Analysis

The results of the biochemical analysis are expressed as mean (±SD). All values were studied using SPSS Statistics for Windows, Version 15.0 (SPSS Inc., Chicago, IL). The descriptive characteristics of study groups were compared using unpaired Student's t test for numerical values and chi- square test for categorical data. Comparisons with a p value <0.05

were accepted as statistically significant. The Kolmogorov- Smirnov test was used to check whether the numeric variables were normally distributed. Cystatin-C, NGAL and creatinine level of the study groups at T0, T1, T2, T3 sampling times were analyzed using repeated measures of ANOVA. The authors calculated the sample size for the analysis of outcomes of the study within 95% confidence interval and statistical power of 80%. Thirty-six samples were calculated for each group for creatinine-T3 sampling value (mean±sd Group Study vs Group Control = 0.9±0.3 vs 1.1±0.3) and also 36 for each group for cystatin C-T3 sampling value (mean±sd for Group Study vs Group Control = 0.7±0.15 vs 0.8±0.15). However, the budget limit for laboratory testing could only afford inclusion of 60 patients in the desired study.

Table 1. Descriptive characteristics of the groups.

	Study group (mean± sd)	Control group (mean± sd)
AGE (year)	64.53±8.51	60.97±10.01
MALE (%)	76.70	70.00
X-CLEMP (minute)	38.47±14.21	41.47±13.83
CPB (minute)	68.03±22.29	69.50±21.81
DRAINAGE (cc)	421.67±305.04	466.67±276.78
EF %	54.00±6.40	50.63±7.65
EUROSCORE II	3.60±1.89	3.33±1.81
EXTUBATION (hour)	10.40±3.59	10.10±3.45
INT CARE STAY (day)	2.90±1.16	2.70±1.02
HOSPITAL STAY (day)	7.37±1.35	7.80±1.90
Graft Number		
1	10.0%	3.3%
2	66.7%	63.3%
3-4	23.3%	33.3%
Blood Product Used (Unite)		
0	30.0%	26.7%
1	50.0%	53.3%
2-3	20.0%	20.0%

p>0.05 for all comparisons
X-Clemp: cross clemp, CPB: Cardiopulmonary Bypass Time, EF: ejection fraction, Int Care: Intensive unite stay day, sd: standard deviation)

RESULTS

TThe study was completed as designed. After randomization of 60 patients, Group S (study group) had 6 women and 24 men and Group C (control group) had 5 women and 25 men. The preoperative, intraoperative and postoperative hemodynamic follow-up characteristics were similar between the groups without any statistically significant difference. The demographic characteristics were shown in Table 2.

Plasma cystatin C levels were statistically different between the groups at all time periods, p=0.001 for time and p=0.583 for groups. Plasma NGAL levels also demonstrated significant intergroup difference at two sampling time, p=0.001 for time and p=0.243 for groups. Plasma creatinin levels were statistically significantly different between the groups at all sampling time periods, p=0.001 for time, p=0.131 for groups (Table 3).

The secondary endpoints of the trial were the comparison of three biochemical parameters of kidney injury including cystatin C, NGAL and creatinine between

Table 1. Exclusion criteria of the patients involving the trial.

- Age >75 years
- Body mass index >35 kg m^{2-1} (because appropriate sized blood pressure cuff was not available)
- Severe peripheral vascular disease (ankle/brachial index in either leg <0.9)
- Severe left ventricular dysfunction (defined as an LV ejection fraction <30% or left ventricular end-diastolic pressure> 16 mmHg)
- Recent myocardial infarction within the previous 4 weeks
- Pulmonary disease (measured Forced Expiratory Volume in 1 second (FEV1) <40% pre-dicted in pulmonary function test)
- Renal (basal serum creatinine >1.5 mg dL^{-1})
- Hepatic dysfunction (total bilirubin >1.2 mg dL^{-1})
- Diabetes mellitus treated with glibenclamide (because of its inhibition of the cardioprotection elicited by RIPC)
- White blood cell count >10,000 mm^{3-1} (indicating infection during the week before surgery)
- Smoking during the month before surgery
- Preoperative use of certain medications (that might have an effect on ischemia-reperfusion injury like antibiotics, beta-blockers, corticosteroids, aspirin, nonsteroidal anti- inflammatory drugs)

Table 3. Metabolic parameters.

	T0	T1	T2	T3	P value*	Study group**	Control group**
Cystatin C							
Study	0.73±0.15*	0.64±0.13*	0.67±0.16*	0.74±0.20*	p=0.001 for time	P=0.002 for T0 vs T1	P=0.071 for T0 vs T1
Control	0.76±0.23	0.71±0.20	0.70±0.25	0.79±0.31	p=0.583 for group	P=0.018 for T0 vs T2	P=0.082 for T0 vs T2
						P=0.860 for T0 vs T3	P=0.593 for T0 vs T3
						P=0.365 for T1 vs T2	P=0.545 for T1 vs T2
						P=0.009 for T1 vs T3	P=0.084 for T1 vs T3
						P=0.003 for T2 vs T3	P=0.030 for T2 vs T3
NGAL							
Study	206.75±59.64	237.81±75.39*	256.76±66.27*	268.85±51.12	P=0.001 for time	P=0.147 for T0 vs T1	P=0.001 for T0 vs T1
Control	203.62±58.24	252.16±49.67	270.27±48.21	266.02±52.34	P=0.243 for group	P=0.014 for T0 vs T2	P=0.001 for T0 vs T2
						P=0.001 for T0 vs T3	P=0.001 for T0 vs T3
						P=0.242 for T1 vs T2	P=0.210 for T1 vs T2
						P=0.047 for T1 vs T3	P=0.333 for T1 vs T3
						P=0.266 for T2 vs T3	P=0.637 for T2 vs T3
Creatinine							
Study	0.80±0.17*	0.77±0.22*	0.90±0.24*	0.90±0.25*	P=0.001 for time	P=0.332 for T0 vs T1	P=0.076 for T0 vs T1
Control	0.82±0.23	0.80±0.25	0.96±0.31	1.07±0.50	P=0.131 for group	P=0.001 for T0 vs T2	P=0.001 for T0 vs T2
						P=0.001 for T0 vs T3	P=0.004 for T0 vs T3
						P=0.001 for T1 vs T2	P=0.001 for T1 vs T2
						P=0.001 for T1 vs T3	P=0.001 for T1 vs T3
						P=0.948 for T2 vs T3	P=0.085 for T2 vs T3

**Repeated measures of ANOVA*
***paired t test*
T0, T1,T2,T3 were the sampling times of the biochemical parameters as in that order:
T0- preoperative, T1- one hour after weaning from CPB, T2- six hours after CPB, T3- twenty-four hours after operation

the groups. We did not observe any difference in regard to superiority of the early detection of AKI.

We observed no significant difference between the groups for any hemodynamic parameters and no patient had any ischemic ECG changes. Cardiac index measurements, requirements for inotropic agents were not different between the groups. The intraaortic pump was not used in any patient. These results assumed that during operation the blood supply of the kidneys did not change to disturb the renal functions. The two groups did not differ in total amounts of drainage, number of blood products used, lengths of intensive care unit stay, hospital stay or postoperative excess mechanical ventilation requirement as shown in Table 2. No operative deaths or serious complications observed in both groups during the perioperative period. No unexpected effects of the RIPC procedure occurred, and no patient had a procedure-related complication.

DISCUSSION

TThe probability of renal function impairment after cardiac surgery changes from 1% to 30% according to diagnostic criterion used and the type of procedure [1]. In previous studies, RIPC application had been demonstrated to have some beneficial outcomes during CABG surgery, surgical repairs of congenital heart defects and percutaneous coronary interventions. There are some studies reporting about some protective effects of RIPC on postoperative renal functions after cardiac surgery and RIPC reportedly decreased incidence of kidney injury after CABG surgery [4,5,7]. Surgery type was also important for the determination of RIPC effect on the kidneys because the coronary, valvular or thoracoabdominal aortic surgery had their own different risk factors for kidney damage. We studied ischemic preconditioning in on-pump patients because renal injury could occur during CPB as a result of complex interactions between the effects of blood viscosity changes due to hemodilution and hypothermia, the absence of blood flow pulsatility and hypotension [2]. The results of our clinical study are not consistent with the findings of these previous studies.

Exposure of tissues to certain periods of sublethal ischemia with consecutive reperfusion periods protects them from the harmful effects of subsequent prolonged ischemia. This application is termed ischemic preconditioning and prepares the tissues for ischemic injuries. The aim of this intervention-ischemic preconditioning is to minimalize reperfusion injury and

preserve endothelial function in the vascular system [20]. The duration and exact technique of RIPC have varied among previous studies, with some using 3 and some using 4 cycles of cuff inflation and deflation. For this study, 3 cycles of inflation-deflation was chosen because of its frequent use by many researchers and clinics.

In our study, RIPC was applied to the more homogenous patient population. One type of surgery was performed to the patients. All anesthetic techniques and surgical methods were the same. Preoperative renal function was evaluated by serum creatinine levels and these results were in normal ranges for the two groups of patients. We applied the RIPC intervention for patients with normal renal function. In the previous studies type of surgery, and patient population were so different that we thought that comments related to RIPC was protective or not, were inappropriate.

We used three biochemical parameters for detecting AKI. The levels of biochemical markers increase according to anatomical site and different mechanisms of acute kidney damage like glomerular, tubular, interstitial and direct toxic affects [12,13]. We did not observe AKI requiring renal replacement therapy in our patients. This could be the result of the low risk profile of the study patients. Creatinine is a marker that has been used for a long time to follow up renal functions. Cystatin C is a protease inhibitor that is synthesized in all nucleated cells at a steady state. It is freely filtered by the glomeruli, not secreted by renal tubules and completely metabolized at the level of the renal tubules. These features have made it a preferred marker of renal functions in kidney injuries. However age, gender, intake of glucocorticoids and high C-reactive protein levels are nonrenal factors that may affect the measurement of plasma cystatin C. NGAL is quickly induced and secreted from the damaged distal nephron. Its level is elevated proportionally according to the severity of renal damage, ischemic renal injury and repair process. Reversely, its level rapidly decreases when the cause of the renal injury disappears. It could be easily measured in both urine and blood. Therefore in this study we measured plasma levels of NGAL [14].

We performed the sampling as 4 times within the first 24 hours postoperatively. These results show us the early effects of RIPC on renal parameters. For the secondary target of the study, to determine the sensitivity of the biochemical markers, the beneficial result of the RIPC procedure could be observed on the creatinine , cystatin C and NGAL levels for short periods of renal function monitoring instead of using inflammatory markers.

Different from the previous trials, we investigated RIPC applied on the patients with normal renal functions or low risk patients in this randomized, controlled, prospective clinical investigation. This is because we did not find any important difference between patients in two groups according to inotropic support, ICU length of stay, and hospital stay. The authors believe that their simple RIPC method should be applied in a diverse group of cardiac surgery patients, even including patients who were using different medications that may affect the protective results of RIPC.

Study Limitations

Because the patients involved in the study were selected carefully (none was using beta-blockers and all were uncomplicated CABG surgery patients), limited number of patients could be enrolled in the study. In addition, financial constraints regarding enzymatic tests prohibited the authors from studying more than 60 patients. The limitations of this study might be the sample size in relation to the large number of variables that can influence the development of IR injury. Further detailed studies with different timing, sampling numbers and intervals, frequency and duration and type of the procedure may be needed. Large series using more sensitive biomarkers which may validate or refute our findings regarding the degree of renoprotective effects of RIPC in this sophisticated area may be needed. For determining the effectiveness of prophylactic application of this procedure the more randomized controlled trials should be performed. Because the study was performed in the operating room, the surgeons were not blinded to the allocation group of the patient. However, laboratory technicians did not know which procedure (inflation or noninflation of the cuff) had been performed on the patients.

The results of this study might differ from other trials because of the details of the procedure used in this

study (eg, inflation-deflation on leg versus arm, frequency of inflation-deflation, duration of inflation). In future studies, measurement of other more sensitive biomarkers may clarify the benefit of prophylactic RIPC on renal function in similar cardiac surgery patients. Because many factors - such as patient age; various medications; and the presence of stable angina, peripheral arterial disease, obesity or diabetes may limit the effectiveness of RIPC [16]. Although these parametres were not considered in the present study some detailed studies should also be plannned whether this procedure is useful in cardiac surgery patients. Large trials would need to show biochemical and clinical benefits of RIPC on kidney before its general use in cardiac surgery patients.

CONCLUSION

In this randomized, controlled trial, RIPC applied to patients with normal renal function undergoing CABG. RIPC was effective in preventing a rise in markers of renal injury, compared with patients not undergoing RIPC. This simple and easy-to-implement method should be used in such patients to protect them from adverse effects of CPB.

Conflict of Interest: None.

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