Remote Ischemic Preconditioning for Prevention of Contrast-induced Acute Kidney Injury in Diabetic Patients

Shokoufeh Savaj, Javad Savoj, Ismail Jebraili, Seyed Hashem Sezavar

[1]Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[2]Rasul-e-Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

Keywords. contrast nephropathy, remote ischemia preconditioning, coronary artery angiography

Introduction. There are some clinical trials showing that short-term ischemia in one organ can protect different organs against higher intensity and longer ischemic insult. We designed a study to assess whether remote ischemic preconditioning (RIPC) on one organ can decrease the rate of contrast-induced acute kidney injury (AKI) in diabetic patients who undergo coronary artery angiography (CAA).

Materials and Methods. This randomized control trial included 96 diabetic patients who were candidates for CAA. Exclusion criteria were congestive heart failure and complications during CAA. All of the patients received 1000 mL of normal saline before CAA. The RIPC group underwent 3 cycles of 5-minute ischemia in their right arm. Serum creatinine was measured before and 24 hours after CAA.

Results. Contrast-induced AKI was reported in 5 cases in the control group and 1 case in the RIPC group (P = .13, odds ratio, 5.4). The differences in serum creatinine level before and after the procedure was significantly lower in RIPC group than that in the control group (P = .04, odds ratio, 0.08). Serum creatinine rise significantly correlated with contrast dose (P = .02) and a history of hypertension (P = .02) in both groups.

Conclusions. Ischemic preconditioning had a protective effect on contrast-induced AKI in our study. Since this method is harmless and cost effective, further studies on patients with chronic kidney disease is required to evaluate addition of ischemic preconditioning to our clinical practice for prevention of contrast-induced AKI.

IJKD 2014;8:457-60
www.ijkd.org

Original Paper

INTRODUCTION

Remote ischemic preconditioning (RIPC), which induces ischemia in one organ, can protect different organs against high-density and longer ischemic attacks. Some studies have shown short cycles of repeated ischemia in the arm can decrease the troponin T release and the size of infarcted tissue after vessel occlusion and reperfusion.[1] There are limited studies to predicate RIPC preventive effect on acute kidney injury (AKI). In one study, Zimmerman and colleagues showed ischemic preconditioning could reduce the relative risk of AKI to 0.43 after coronary artery bypass surgery.[2] Contrast media are a well-known risk factor for AKI, especially in diabetic patients, after coronary artery angiography (CAA).Contrast-induced AKI increases mortality, morbidity, and hospital stay in intensive care unit.[3] We designed a study to assess the effect of RIPC on decreasing the risk of contrast-induced AKI in diabetic patients who undergo CA.

MATERIALS AND METHODS

This study included 96 outpatient diabetic patients who were candidates for CAA in Rasoul-e-Akram General Hospital from2011 to 2012. Exclusion criteria were congestive heart failure and any complications during angiography. The patients were randomized into two groups (control and RIPC groups). All of the patients received 1000 mL of normal saline before CAA. Diuretics, angiotensin II inhibitors, and angiotensin-converting enzyme inhibitors were discontinued 1 day before CAA. After filling the informed consent forms, the study group patients underwent RIPC in their right arms by sphygmomanometer inflation cycles 15 minutes prior to the CAA, which continued until the end of the process. In each cycle, the sphygmomanometer cuff was inflated on the right arm to the point of 200 mm Hg pressure for 5 minutes and then it was deflated. Three cycles were repeated. Serum creatinine was checked before CAA as the basic kidney function test and then 24 hours after the angiography to compare for possible changes. Acute kidney injury was defined as a 30% rise or 0.3 mg/dL increase of serum creatinine level based on the Kidney Disease Improving Global Outcomes guidelines.[4]

All data were extracted from charts and patients. We used the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). The paired *t* test was used to compare serum creatinine levels before and after CAA. We used the chi-square test and independent *t* test for qualitative and quantitative variables to compare confounding factors between two groups. A P value less than .05 was considered significant.

RESULTS

There were 48 patients in each group. The mean age of the patients was 62.0 ± 9.3 years and there were 31 women and 65 men participating in the study. There were no significant differences in age, sex, estimated glomerular filtration rate, radiocontrast dose, and a history of myocardial infarction, cerebrovascular accident, and hypertension between the two groups (Table 1). Serum creatinine did not change significantly in the RIPC group (*P* = .30), but a significant increase was observed in the control group (*P* = .04; Table 1; Figure). The difference in serum creatinine level before and after the procedure was significantly lower in the RIPC group than that in the control group (*P* = .04; odds ratio, 0.08). Acute kidney injury was reported in 5 cases in the control group compared to 1 case in the RIPC group (*P* = .13;

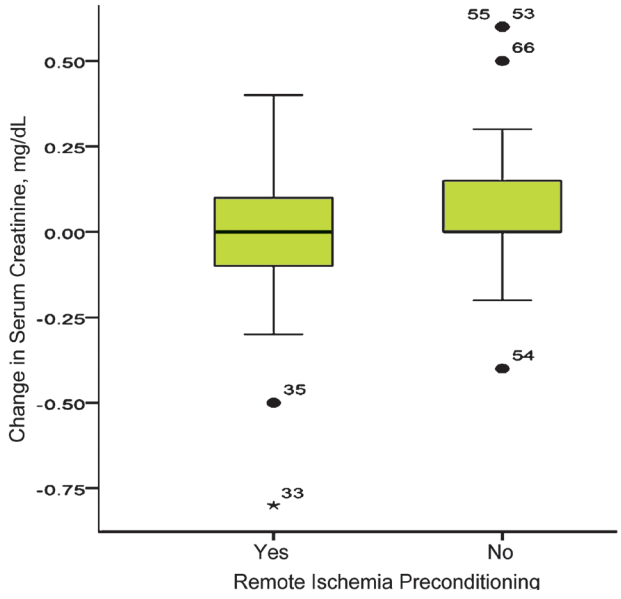
Table 1. Patients' Characteristics and Risk Factors of Contrast-induced Acute Kidney Injury in te Study Groups*

Characteristic	RIPC Group	Control Group	*P*
Sex			
Male	17	14	
Female	31	34	.60
Mean age, y	63.0 ± 8.9	60.9 ± 9.6	.27
Contrast dose, mL	126.6 ± 77.2	123.8 ± 66.6	.85
Baseline GFR, mL/min	78.2 ± 25.8	94.7 ± 40.2	.02
Baseline serum creatinine, mg/dL	1.3 ± 0.4	1.1 ± 0.3	.02
History of hypertension, %	66.7	75.0	.50
History of myocardial infarction, %	20.8	12.5	.27
History of CVA, %	4.2	6.3	> .99
Diabetic retinopathy, %	6.3	2.1	.61
GFR < 60 mL/min, %	23.0	18.0	.41

*RIPC indicates remote ischemic preconditioning; GFR, glomerular filtration rate and CVA, cerebrovascular accident.

Table 2. Changes in Serum Creatinine in the Remote Ischemic Preconditioning (RIPC) and Control Groups

	Serum Creatinine		
Study Group	Before Angiography	After Angiography	*P*
RIPC	1.28 ± 0.40	1.25 ± 0.40	.30
Control	1.10 ± 0.30	1.16 ± 0.50	.04



Differences in serum creatinine before and after contrast nephropathy in the remote ischemia preconditioning and control groups.

Table 3. Changes in Serum Creatinine Levels by Risk factors in the Study Groups

	RIPC Group		Control Group	
Risk Factor	Creatinine Change	*P*	Creatinine Change	*P*
Glomerular filtration rate < 60 mL/min	-0.10 ± 0.22	.57	0.04 ± 0.24	.56
History of myocardial infarction	0.00 ± 0.20	.60	0.05 ± 0.08	.50
History of hypertension	-0.03 ± 0.20	.02	0.08 ± 0.20	.02
Contrast dose > 60 mL	-0.03 ± 0.20	.02	0.06 ± 0.19	.02
Age > 65 years	-0.06 ± 0.20	.18	0.02 ± 0.20	.17
Male sex	-0.01 ± 0.10	.23	0.08 ± 0.30	.27
Female sex	-0.03 ± 0.30	.06	0.05 ± 0.20	.07

odds ratio, 5.4). Serum creatinine rise significantly correlated with contrast dose (P = .02) and a history of hypertension (P = .02) in all of the patients, but there were no significant differences between the two groups (Table 3).

DISCUSSION

The administration of contrast media can lead to a usually reversible form of acute kidney failure that begins soon after the contrast is administered. Many important issues remain unresolved including the pathogenesis of the disorder and relative efficacies of various prophylactic strategies. A large body of evidence related to the pathogenesis of contrast nephropathy comes from animal models. The two major theories are renal vasoconstriction resulting in medullary hypoxemia, possibly mediated by alterations in nitric oxide, endothelin, and adenosine, and direct cytotoxic effects of the contrast agents.[5]

Among patients who undergo contrast administration, a more marked decline in glomerular filtration rate occurs primarily in patients with renal insufficiency, diabetic nephropathy, congestive heart failure, and multiple myeloma, as well as those who undergo percutaneous CAA.[6-9] Among all available strategies for prevention of acute kidney injury in patients at risk for contrast nephropathy, isotonic intravenous hydration is the most beneficial preventive method. The selection of fluid and rate of administration must take into consideration, as well as the patient's ability to tolerate the fluid load (eg, rapid volume expansion may be harmful to individuals with reduced left ventricular function), the ability to tolerate alkalinization, and the degree of underlying risk for nephropathy.

Most of diabetic patients who undergo CAA have some levels of even subclinical heart and kidney dysfunction. Therefore, administration of intravenous fluid may have some limitations in such patients. Based on this fact, many other preventive methods have been tried to eliminate AKI after contrast administration in these patients. One of these methods is RIPC, which we used in our study. Experimental studies have demonstrated that the heart, liver, lung, intestine, brain, kidney, and limb are capable of producing remote preconditioning when subjected to brief ischemic reperfusion injury.[10] Abdel-Kader and colleagues conducted a randomized study of 100 patients with kidney dysfunction who were candidates for elective angiography.[11] They showed that contrast-induced AKI occurred in 26 patients, 20 in the control group and 6 in the RIPC group (odds ratio, 0.21; 95% confidence interval, 0.07 to 0.57; P = .002).[11]

According to the previous studies, it seems that RIPC stimulus presumably induces release of biochemical messengers which act either by the bloodstream or by the neurologic pathway. Therefore, ischemic preconditioning in one organ releases these biochemical messengers which act on the other organ.[11] Igarashi and coworkers concluded in an study on 60 patients with moderate chronic kidney disease that RIPC alleviated contrast-induced AKI in patients at low to moderate risk by decreasing oxidative stress and plasma asymmetrical dimethyl arginine.[12] All ischemic conditionings share a common pathway on mitochondria. Molecular triggers (pharmacological, autacoids, or neural stimulation) activate Gprotein coupled receptors which leads to the activation of signaling protein kinases and the opening of mitochondrial adenosine triphosphate-sensitive potassium channels and inhibit the formation of the mitochondrial permeability transition pore which is a key step in protecting cell from death.[13] Other protective mechanisms include suppression of the inflammatory response by increased nitric

oxide release and increased expression of heat shock proteins, which reduces cytokine release and results in cytoprotection.[14]

In this study, we could that show RIPC had a protective role in prevention of contrast-induced AKI. More than 50% of our study population had an estimated glomerular filtration rate more than 60 mL/min, which would put them in a low-risk probability of contrast-induced AKI. We suppose that this protective effect could be more prominent in advanced CKD stage.

CONCLUSIONS

Ischemic preconditioning showed a protective effect against contrast-induced AKI in our study. Since this method is harmless and cost effective, further clinical trials are required to be designed to evaluate ischemic preconditioning method for contrast-induced AKI prevention in chronic kidney disease patients.

ACKNOWLEDGEMENTS

We appreciate the excellent collaboration of the angiography team of Rasoul-e-Akram Hospital during the study.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Shokoufeh Savaj, MD
Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
E-mail: ssavaj@hotmail.com

Received December 2013
Revised April 2014
Accepted April 2014