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The role of remote ischemic preconditioning in preventing contrast-induced nephropathy following invasive coronary angiography; a randomized controlled trial

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ABSTRACT

Introduction: Remote ischemic preconditioning (RIPC) is now proposed as an effective approach for preventing contrast-induced nephropathy (CIN); however, the results on its efficacy have already remained uncertain.

Objectives: We aimed to assess the beneficial effects of RIPC in preventing CIN in patients undergoing coronary angiography (CA) followed by angioplasty.

Patients and Methods: One hundred patients candidate for elective CA and coronary angioplasty, moderate to high risk for CIN were randomized into two groups including the group which planned for RIPC, and the control group. The overall prevalence rate of CIN was assessed and compared across the two groups.

Results: The two groups were matched for demographics, cardiovascular risk profiles and laboratory parameters. The prevalence of CIN in RIPC group was 14.0% and in the control group was 26.0% indicating no statistical difference between the two groups (P = 0.105). Requiring dialysis was also planned for 0.0% and 2.0% respectively with no difference (P = 0.500).

Conclusion: RIPC may not prevent CIN in patients who are candidate for invasive CA.

Trial Registration: The study was approved in the Iranian Registry of Clinical Trials (identifier: IRCT20171230038144N1; https://www.irct.ir/trial/28715, ethical code: IR.IUMS.FMD.REC 1396.9311171014).

Implication for health policy/practice/research/medical education:
In the current RCT on 100 patients candidate for elective coronary angiography and angioplasty, we found RIPC may not prevent CIN in patients who are moderate to high risk for contrast induced nephropathy after invasive coronary angiography.

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Introduction

Cardiac catheterization as a standard diagnostic modality is now routinely employed in all cardiovascular centers in almost all patients suspected to coronary involvement. In this regard, despite improving high diagnostic performance of other non-invasive modalities such as coronary CT angiography, none of them could be replaced the conventional invasive coronary angiography; however, some patients who undergoing this invasive diagnostic procedure, face procedural-related complications as major complications in up to 2% and even death in about 0.08% (1). One of the main potential limitations of invasive CA refers to the use of contrast, as nephropathy induced by these agents or contrast-induced nephropathy (CIN). Despite conducting several human and animal experimental studies on the reasons of such event, its pathophysiology has already remained uncertain. It seems that contrast agents can injure kidney by inducing medullary hypoxia through flaring-up reactive oxygen species (ROS) and free radicals leading to tubular cell toxicity and thus medullary ischemia (2,3). Moreover, contrast agents can reduce regional microcirculatory

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blood flow, leading higher oxygen demand of tubular cells (4). In this regard, it seems a close link of the osmolality of the contrast medium with severity of medullary hypoxia and thus intensity of kidney injury (5).

One of the suspicious approaches to prevent occurrence of CIN is remote ischemic preconditioning (RIPC) which is defined as transient brief episodes of ischemia at a remote site before a subsequent prolonged ischemia/reperfusion injury of the target organ (6). This approach is an adaptive response that can protect the organs against any ischemic and reperfusion defects. According to different reports, using this method could reduce the likelihood of CIN in patients suffering mild to moderate renal defects (7). According to the report by Er et al (8), RIPC performed as 4 cycles of 5 minutes ischemia/5 minutes reperfusion of the upper limb by inflation/deflation of a blood pressure cuff prior to contrast exposure could effectively reduce the risk for CIN by 40%. Such benefits have been also revealed by Deftereos et al (9). They showed, following the use of RIPC in patients suffering non-ST elevation myocardial infarction who candidate for CA leading, a 29.5% reduction in the risk for CIN was detected.

Objectives

In line with the previous observations, we aimed to assess the beneficial effects of RIPC in preventing CIN in patients undergoing CA followed by angioplasty.

Patients and Methods

Study population

Among patients aged ≥18 years referred to outpatient interventional cardiology clinic, according to the previous study by Er et al (8) that showed incidence of CIN 12% in study group compared to 40% in control group, 50 patients were included in each group (Figure 1). Therefore one hundred patients were enrolled according to the following inclusion criteria (October 2017 to February 2018); willing to be enrolled in the study, candidate for elective CA and coronary angioplasty, moderate to high risk for CIN according to the Mehran score (10). The patients were excluded in case of having at least one of the following conditions; participating in another trial during the last three months, contrast media exposure during the last month, pregnancy, scheduling peritoneal and hemodialysis, CA due to valvular and congenital heart disease, impossibility of doing RIPC due to trauma, the presence muscle dystrophy or any vascular complication. CIN was defined as a 25% increase in serum creatinine from baseline or a 0.5 mg/dL increase in its absolute value within 24-72 hours after intravenous contrast administration.

Study protocol

A thorough clinical history was obtained and a comprehensive physical examination was conducted for all study participants, the physical performance and upper limb exam was conducted in all. The patients were then randomized (using the balanced block randomization with Random Allow version 1.2 software) into two groups including the group which planned for RIPC and the control group. As the initial performance, oral N-acetyl

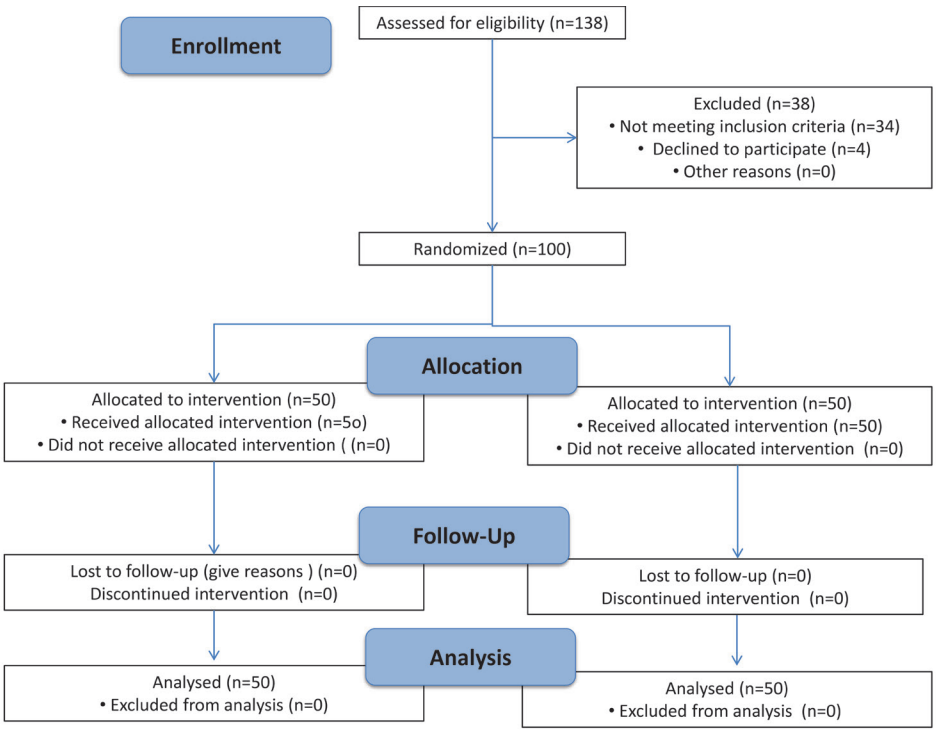

Figure 1. CONSORT flow diagram of the study.

cysteine (1200 mg twice orally, the day before and on the day of CA and angioplasty) was infused and then continuous intravenous saline 0.9% (1 mL/kg/weight/hour) was infused 12 hours before to 12 hours after CA and angioplasty. The use of nephrotoxic drugs (such as aminoglycosides, non-steroidal anti-inflammatory drugs, calcineurin inhibitors or metformin) was prohibited. RIPC was accomplished in 50 patients by performing four cycles of alternating 5-minute inflation and 5-minute deflation of a standard upper-arm blood pressure cuff to the individual's systolic blood pressure plus 50 mm Hg to induce transient and repetitive arm ischemia and reperfusion. RIPC was started in the waiting room just before transferring to procedural room for CA and percutaneous coronary angioplasty (PCI). The time between the last inflation cycle and the start of CA was 60 minutes. The control group including 50 patients was planned for RIPC in the same way but by inflating an upper-arm blood pressure cuff to diastolic pressure levels and then deflating the cuff for 10 mm Hg to maintain non-ischemic upper-arm compression for blinding purposes with regard to the patients.

Study measurements

Biochemical measurements were conducted at baseline and daily and in 3-7 days after the procedure. Whole blood was collected from all study participants after 12 hours overnight fasting. The laboratory tests including complete blood count (CBC), serum hemoglobin level, blood urea nitrogen (BUN), the baseline serum creatinine level the day before the procedural and then on first day, second, third and in 2-7 days after procedure, serum electrolytes (sodium, potassium), fasting blood glucose, lipid profiles and urinary output before and after the procedure. Two-dimensional (2D) conventional, pulse and transthoracic echocardiographic study was conducted with commercial GE Vivid seven System (Horten, Norway) for all patients following the procedural interventions.

Statistical analysis

Data are presented as frequencies, mean ± standard deviation (SD) or median ± interquartile range (IQR) as appropriate. For statistical analysis, the *t* test or Mann-Whitney U test was used to compare quantitative variables with normal and abnormal distribution, respectively. The chi-square test or Fisher's exact test was also employed to compare categorical variables. G*Power 3.1 software was applied to calculate statistical power ($\alpha = 0.05$, and $\beta=0.1$). All analyses were conducted using IBM SPSS statistics 24 for windows (IBM Corp., Armonk, NY, USA).

Results

The baseline clinical and laboratory parameters are described in Table 1. The average age of participants was 66.00 ± 7.75 years and 777% were male. The most common cardiovascular risk factor was hypertension (87%) followed by diabetes mellitus (52%). Notability, 72% suffered from heart failure. Comparing baseline parameters including demographics, medical history and laboratory findings (Table 2) showed no difference across the two RIPC and control groups. Echocardiography assessment in RIPC and control groups showed mild left ventricular dysfunction in 46% and 40%, moderate left ventricular dysfunction in 22% and 28% and severe left ventricular dysfunction in 10% and 10% respectively ($P=0.863$). In addition, mild, moderate and severe right ventricular dysfunction was found in 48%, 50% and 2% in the RIPC group and 52%, 44% and 4% in the control group with no difference between the two groups ($P=0.922$). In CA, single, two and three vessels involvements were found in 34%, 32%, and 32% in the RIPC group and 28%, 32%, and 36% in the control group with no significant statistical difference ($P=0.863$). In the RIPC and control groups, percutaneous coronary intervention on left anterior descending was scheduled in 73.3% and 62.5%, on left circumflex in 12.5% and 10.0% and on right coronary artery in 16.7% and 25.0% respectively ($P=0.685$). Regarding ultimate therapeutic approach, coronary artery bypass graft surgery was considered in 30.0% and 38.0% ($P=0.263$). Overall, the prevalence of CIN in the RIPC group was 14.0% and in the control group was 26.0% indicating no statistical difference between the two groups

Table 1. The baseline clinical and laboratory parameters (n = 100)

Variable	
Age, mean ± SD	66.00 ± 7.75
Male gender, N (%)	77 (77)
Hypertension, N (%)	87 (87)
Dyslipidemia, N (%)	55 (55)
Diabetes mellitus, N (%)	52 (52)
Smoking, N (%)	39 (39)
Thyroid disease, N (%)	8 (8)
Anemia, N (%)	43 (43)
Heart failure, N (%)	73 (73)
FBS (mg/dL), mean ± SD	129.44 ± 5.32
HBA1c %, mean (SD)	8.11 ± 1.21
TG (mg/dL), mean ± SD	146.25 ± 5.25
Cholesterol (mg/dL), mean ± SD	138.21 ± 3.73
HDL (mg/dL), mean ± SD	33.36 ± 0.78
LDL (mg/dL), mean ± SD	74.71 ± 2.04
HB (mg/dL), mean ± SD	11.89 ± 2.21
BMI, mean ± SD	27.72 ± 0.23
EF %, mean ± SD	41.40 ± 0.93
Base line Cr (mg/dL), mean ± SD	1.52 ± 0.02
Base line BUN (mg/dL), mean ± SD	26.26 ± 0.91

BUN: blood urea nitrogen, Cr: creatinine, Hb: Hemoglobin, FBS: fasting blood glucose, TG: triglyceride, Chol: cholesterol, LDL: Low-density lipoprotein, HDL: high density lipoprotein, BMI: body mass index, EF: ejection fraction, GFR: glomerular filtration rate.

Table 2. Comparing risk factors and demographic data in two RIPC and control group

Variable	RIPC (n = 50)	Control (n = 50)	*P* value
Age	68 (62-71)	67 (617-71)	0.455
Male gender	41 (82%)	36 (72%)	0.171
Hypertension, N (%)	44 (88%)	43 (86%)	0.500
Dyslipidemia, N (%)	31 (62%)	24 (48%)	0.114
Diabetes mellitus, N (%)	29 (58%)	23 (46%)	0.158
Smoking, N (%)	20 (40%)	19 (38%)	0.500
Thyroid disease,N (%)	2 (4%)	6 (12%)	0.134
Anemia, N (%)	21 (42%)	22 (44%)	0.500
Heart failure ,N (%)	36 (72%)	37 (74%)	0.500
Post CABGs,N (%)	6 (12%)	4 (8%)	0.254
Post PCI,N (%)	8 (16%)	9 (18%)	0.500
Proteinuria,N (%)	10 (20%)	5 (10%)	0.131
FBS (mg/dL), median (IQR)	112 (96-158)	104 (94-151)	0.959
HBA1c %, median (IQR)	8.5 (6.9-8.9)	8.5 (7.2-8.8)	0.915
TG (mg/dL), median (IQR)	145 (107-172)	141 (114-168)	0686
Chol (mg/dL), median (IQR)	143 (121-162)	141 (119-157)	0.454
HDL (mg/dL), median (IQR)	34 (30-37)	35 (30-38)	0.795
LDL (mg/dL), median (IQR)	75 (60-92)	70 (60-86)	0.434
HB (mg/dL), median (IQR)	13.55 (12.17-14.30)	13.45 (123.5-14.15)	0.258
BMI, median (IQR)	27.7 (26.1-29.4)	26.9 (26.3-29.7)	0.896
EF %, median (IQR)	40 (35-50)	40 (35-50)	0.919
Contrast media (cc), median (IQR)	140 (110-170)	145 (110-170)	0.686
Cr (mg/dL), median (IQR)	1.5 (1.4-1.6)	1.4 (1.4-1.52)	0.392
BUN (mg/dL), median (IQR)	24 (21-30)	22.5 (20-30)	0.363
GFR cc/min, median (IQR)	44 (38-51)	45 (39-52)	0.817
Second cr (mg/dL), median (IQR)	1.5 (1.4-1.6)	1.5 (1.4-1.6)	0.389
Second BUN (mg/dL), median (IQR)	24 (21-31)	24 (20-30)	0.712
Second GFR cc/min, median (IQR)	48 (36-50)	45 (39-50)	0.751
Third Cr (mg/dL), median (IQR)	1.4 (1.3-1.62)	1.5 (1.4-1.72)	0.110
Third BUN (mg/dL), median (IQR)	21 (18-28)	24 (19-29)	0.221
Third GFR (cc/min), median (IQR)	46 (39.75-51.25)	44 (36.75-51)	0.341
Urinary output (cc/daily)	2400 (2075-2820)	2400 (2100-2750)	0.902

BUN: Blood urea nitrogen, Cr: creatinine, Hb: Hemoglobin, FBS: fasting blood glucose, TG: triglyceride, Chol: cholesterol, LDL: low-density lipoprotein, HDL: high density lipoprotein, BMI: body mass index, EF: ejection fraction, GFR: glomerular filtration rate, IQR: interquartile range; PCI: percutaneous coronary angioplasty, CABGs: coronary artery bypass graft surgery.

($P = 0.105$). Requiring dialysis was also planned for 0.0% and 2.0% respectively for the groups with no difference ($P = 0.500$).

Discussion

The preventive effects of RIPC on CIN are unclear since the results of clinical studies are paradoxical. As clearly found in the present study, although the prevalence rate of CIN seems to be numerically lower in the RIPC group compared to the control group, this difference remained insignificant statistically. Although such insignificant results may be due to ineffectiveness of the relevant protocol, our small sample size and thus partially low power may affect our result. However, in line with some previous studies, RIPC may not be effective in correction of CIN in patients who are candidate for CA.

It should be also pointed that, the included samples were high risk for CIN according to Mehran score, while in some studies which confirming effectiveness of RIPC, their patients were low risk for such complication. In a meta-analysis by Hu et al (11), systematically reviewing the literature showed that RIPC significantly decreased the likelihood of contrast-induced AKI. In their final analysis, random effects meta-regression also showed that RIPC tended to strengthen its renoprotective effect. In the study by Igarashi et al (12), RIPC alleviated CIN inpatients at low-moderate risk. In another study by Er et al (8), RIPC planning before using contrast medium could prevent CIN even in high-risk patients, which was inconsistent with our results. In the randomized control trial study by Savaj et al (13), the differences in serum creatinine level before and after the procedure was

significantly lower in the RIPC group than that in the control group. They showed that serum creatinine rises, significantly correlated with contrast dose and a history of hypertension. In addition, in a meta-analysis by Pei et al (14), RIPC was shown to offer cardiorenal protection and the pointed effect was more pronounced in male subjects. In another systematic review by Hu et al (15), RIPC significantly increased the minimum eGFR in the CIN subgroup as compared with the control group. In addition, the length of ICU stay in the RIPC group was significantly shorter than in the control group. Furthermore, the report by Elserafy and colleagues (16), showed the incidence of CIN was markedly lower in ischemic preconditioning group 14% versus 38% in control group. Although the study conducted by Valappil et al (17) revealed significant improvement in the post procedure creatinine values and glomerular filtration rate within six weeks of procedure in RIPC group, the secondary outcome composite of requirement of hemodialysis, death and rehospitalization for heart failure was not statistically significant.

Despite the previous study, in the present study we did not find any differentiation of CIN between two groups in high-risk patients with serum creatinine level more than 1.4 mg/dL or glomerular filtration rate ≤60 mL/min/1.73 m^2. In all of our patients we considered hydration and using NAC before procedure due to previous valid data and it may have preventive effect of CIN in these patients; however, it may be a confounding factor for evaluation of RIPC in our patients.

Conclusion

It can be finally concluded that RIPC may not have a major role in preventing CIN in patients who are candidate for CA. Our finding might be affected by the small sample size. In addition, the pointed preventive role may be influenced by the patients' risk stratification for CIN also the dosages of preoperative medications for preventing CIN that all should be considered in further studies.

Authors' contribution

Conceptualization: ZS. Methodology: MP, HR and ZS. Validation: MP, HR and ZS. Formal Analysis: MP, HR and ZS. Investigation: ZS. Resources: MP, HR and ZS. Data Curation: ZD and HR. Writing—Original Draft Preparation: MP, HR and ZS. Writing—Review and Editing: MP, HR and ZS. Visualization: MP, HR and ZS. upervision: MP, HR and ZS. Project Administration: MP, HR and ZS.

Conflicts of interest

There were no conflicts of interest to declare.

Ethical issues

The research was approved by research and ethics committee of Rajaie cardiovascular medical and research center and registered in the Iranian registry of clinical trials (identifier: IRCT20171230038144N1). The written informed consent was obtained from all patients. Accordingly, the research was part of MD thesis of Hoda Rafieijelodar at Iran University of Medical Sciences supported by the university and ethical issues completely observed by the authors.

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