Original Article

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Remote Ischemic Preconditioning to Prevent Contrast-Associated Kidney Injury in Elective Coronary Angiogram: A Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: Remote ischemic preconditioning (RIPC) is a new strategy to prevent organ injury from oxidative stress and ischemic reperfusion injury, particularly for the kidney, heart, and brain. Contrast-associated acute kidney injury (CA-AKI) is a complication of coronary angiography (CAG). Based on previous studies, whether RIPC prevents CA-AKI post-CAG remains unclear. Therefore, this study aims to compare the efficacy of standard (std) management and standard management with RIPC to prevent CA-AKI post-CAG.

METHODS: This study was an open-label 1:1 randomized controlled trial. The elective CAG patients with an estimated glomerular filtration rate of 15–45 mL/min/1.73 m^2 were enrolled. For the RIPC group, patients performed RIPC starting from inflating manual cuff pressure to 200 mmHg for 5 min on an extremity and then deflating 5 min alternate to four times before coronary angiogram at least 1 hr. All patients had received the usual standard management of pre-CAG. The AKI outcomes were evaluated at 48 hrs and 1 week post-CAG. The adverse events were also assessed.

RESULTS: A total of 27 patients (RIPC group = 14, std group = 13) were enrolled in this study. Baseline characteristics were comparable between both groups except for male gender was higher in the RIPC group (std group 7 [53.85%] and RIPC group 11 [78.57%]), in part of the amount of contrast media volume and procedure duration was higher in the std group (mean contrast volume are 140 [120] mL in the std group and 40.00 [31.25] mL in the RIPC group). No AKI event was observed in the RIPC group. By contrast, AKI in the std group at 48 hrs included two (15.4%) participants and one (7.7%) participant at 1 week. Serious adverse events were not observed in both groups.

CONCLUSION: RIPC may be implemented as a systematic strategy to prevent CA-AKI post-CAG. Some researchers tend to improve CA-AKI. Further studies in a larger number of participants may verify the benefit of RIPC and provide definite conclusion.

KEYWORDS: acute kidney injury, contrast media, coronary angiogram, remote ischemic preconditioning

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INTRODUCTION

Contrast-associated acute kidney injury (CA-AKI) is the third most common cause of hospital-acquired acute kidney injury (AKI) caused by the frequent use of contrast media for diagnostic tools and most intervention procedures[1]. Diagnosis of CA-AKI is indicated by the increase of serum creatinine level after exposure to contrast media and exclusion of another causes[2]. The incidence of CA-AKI varies in several studies, accounting for 9.1%–31.9%[3-4].

The mechanism of CA-AKI is not well proven but perhaps from direct toxic to renal cellular and renal hemodynamic modification as intrarenal vasoconstriction[5]. Contrast media produce oxygenated free radicals and proinflammatory cytokines, which cause AKI and acute tubular necrosis[6-7]. However, using contrast media may affect high-risk patients, particularly those with chronic kidney disease (CKD), and a higher Mehran's risk score, which evaluates the risk of CA-AKI[8-9].

A previous large recent clinical trial has shown no benefit of N-acetylcysteine in CA-AKI[10]. In addition, a strategy to prevent CA-AKI remains unknown. Since 1993, remote ischemic preconditioning (RIPC) was studied to prevent myocardial ischemia after coronary artery bypass surgery and percutaneous coronary artery intervention[11]. The principle of RIPC is making repeated transient nonlethal ischemia and reperfusion to produce various mediators for physiological adaptation to tissue hypoperfusion[5,7]. The signal of transduction in RIPC cascades through the phosphoinositide 3-kinase/Akt (Protein kinase B)/endothelial nitric oxide synthase/cyclic guanosine monophosphate/PKG (Protein kinase G) pathway, thereby leading to the opening of the ATP-dependent mitochondrial potassium (K_{ATP}) channel. The activated mitochondrial K_{ATP} channels can limit the opening of mitochondrial permeability transition pores, thereby causing a marked improvement in cell survival[12]. Some studies suggest that CA-AKI may be due to anti-inflammatory or antioxidant effects, including decreased extracellular levels of noxious metabolites, by activating tumor necrosis factor receptor and promoting the production of manganese superoxide dismutase, a potent antioxidant and protector against reactive oxygen species[13-14]. Moreover, RIPC decreases the generation of free radicals such as xanthine oxidase activity[11].

Based on previous studies, numerous studies have shown the benefit of RIPC in preventing CA-AKI[3,5,11]. However, the data from the AKI high-risk group are scarce. Hence, the efficacy of RIPC for the prevention of AKI in patients who underwent elective CAG was explored in this study.

METHODS

This study was an open-label 1:1 randomized controlled trial conducted at a university hospital located in Bangkok, Thailand. The first date of enrollment was May 2020. This study was early terminated in January 2021 because of the following factors: (1) low rate of enrollment caused by the Coronavirus disease 2019 (COVID-19) pandemic and (2) low incidence of CA-AKI.

The inclusion criteria were as follows: at least 18 years of age, scheduled for an elective coronary angiogram, and the estimated glomerular filtration rate (eGFR) was stable at 15–45 mL/min/1.73 m^2 for at least 3 months. eGFR was calculated by CKD-EPI equation, expressed as a single equation: GFR = 141 * min (Scr/κ,1)$^{\alpha}$ * max (Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} * 1.018 (if female) * 1.159 (if black).

However, given the small number of enrolled participants than expected, the inclusion criteria were amended by adding adjusting criteria to (1) eGFR <60 mL/min/1.73 m^2 and age >60 years old or (2) diabetes mellitus in June 2020. The critical exclusion criteria were as follows: AKI, congestive heart failure or acute myocardial infarction, active infection, history of recent nephrotoxic drug in the previous 3 months, and limb-amputated patients. The full inclusion and exclusion criteria were published in the

Thai clinical trial registry (TCTR20200526009). After enrollment, participants were randomly allocated to receive standard management or standard management with RIPC by using a block-of-four technique. The standard management group received isotonic intravenous hydration before the intervention and continued current medication. Blood pressure level was controlled to below 160/90 mmHg. We also controlled blood sugar at 80–140 mg/dL. Furthermore, they were checked, and the use of nephrotoxic drugs was discontinued. In RIPC, the procedure was performed by an investigator. The RIPC procedure[5] starts from inflating standard manual cuff pressure to 200 mmHg for 5 min on the left arm of the participant and then deflating 5 min alternate to four times before the coronary angiogram for at least 1 h (figure 1). All participants also received standard management to prevent CA-AKI.

The primary outcome was AKI, defined as an increase in serum creatinine level by ≥0.3 mg/dL within 48 hrs or an increase in serum creatinine level to ≥1.5 times baseline, which is known or presumed to have occurred within the last 7 days in accordance with the KDIGO guidelines[2]. Secondary outcomes were as follows: (1) the incidence of acute hemodialysis and (2) death. Serious adverse events and any adverse events were observed for 7 days. Specific adverse events included ischemic limb, presence of petechiae, and hematoma present at the extremity of patients who performed RIPC.

STATISTICAL ANALYSIS

Er *et al*.[14] reported that CA-AKI occurred in 40% of the patients in the control group but only 12% of the patients in the RIPC group (P = 0.002). We calculated the sample, and the result was compared between the two populations[15] with a confidence level 0.95, power 0.8, and dropout rate of 10%. The sample size was 40 patients for each group.

All continuous data were tested for normal distribution by using the Shapiro–Wilk test. We reported the mean ± standard deviation for normal distribution data and median (interquartile range) for otherwise. We compared the mean and median between the two groups by T-test and Mann–Whitney U test, respectively. Categorical data were presented in number and percentage by comparing using Chi-square test or Fisher's exact test depending on appropriateness. We performed modified intention-to-treat analysis for patients who follow-up after CAG at 48 hrs. Laboratory results for participants who lost follow-up on the 7th day after enrollment were obtained and analyzed using last observation carried forward. Statistical analysis was performed by Python version 3.7.10 (library-package: Pandas, 1.1.5; Numpy, 1.19.5; and Statsmodels, 0.11.1). A p-value of <0.05 was a threshold of statistical significance.

This study was approved by the research ethics committee of the Vajira Hospital, COA 150/2562. The trial was performed under the principles of the Declaration of Helsinki[17]. In addition, this trial was registered at the Thai Clinical Trials Registry (TCTR20200526009).

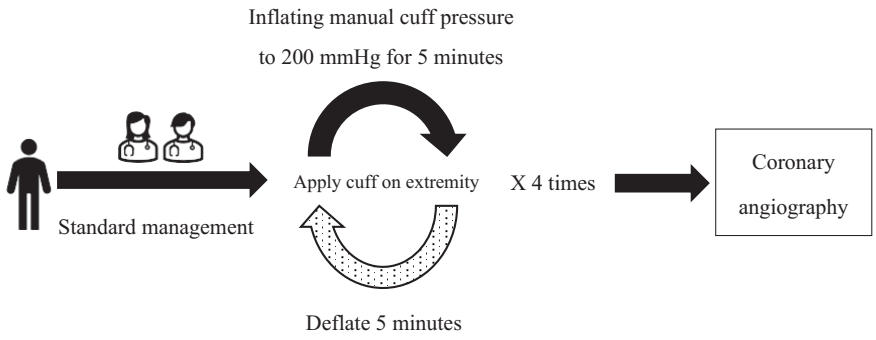

Figure 1 RIPC procedure

RESULTS

From June 2020 to January 2021, a total of 141 patients underwent screening (figure 2). Twenty-seven patients were randomly allocated to the standard management group (std group) with 13 patients and the RIPC group with 14 patients.

Baseline characteristics were primarily balanced between the two groups (table 1). The average age was 68 years old. The most common comorbidities were hypertension (85.1%), coronary artery disease (66.7%), and dyslipidemia (63.0%). Many participants in the std group had dyslipidemia and lower body weight. Current medications and laboratory baseline between the two groups were similar. However, in the CAG procedure, the amount of contrast media and procedure duration were significantly higher in the std group (mean contrast volume is 140.00 [120.00] mL in the std group and 40.00 [31.25] mL in the RIPC group).

The primary outcome was AKI at 48 hrs, which did not occur in the RIPC group. However, two (15.4%) events occurred in the std group (table 2). Both participants had AKIN stage 1. After CAG for 1 week, only one AKI event occurred in the std group. The serum creatinine level was not statistically different between the two groups at 48 hrs and the end of the study. However, eGFR at 48 hrs and the end of the study were higher in the RIPC group. No incidence of initiated hemodialysis or death occurred during the study.

Serious adverse events such as an ischemic limb, presence of petechiae, and presence of hematoma at the affected extremity were not observed during the study period.

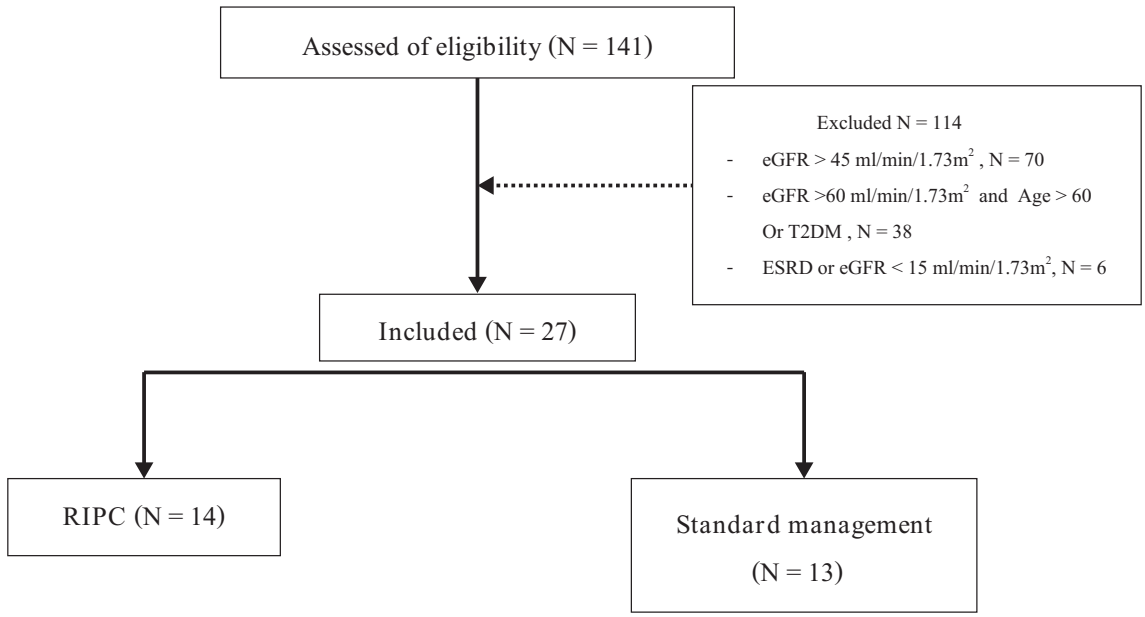

Figure 2 Consort flow diagram of randomization

Abbreviations: CAG, coronary Angiogram; N, number of participants; RIPC, remote ischemic preconditioning

Table 1 Baseline characteristics of participants*

characteristics	Total	Std-group	RIPC	P-value
N	27	13	14	
Age, years	68.67 (±6.99)	69.54 (±7.48)	67.86 (±6.41)	0.551
Male; N (%)	18 (66.67%)	7 (53.85%)	11 (78.57%)	0.173
Hypertension; N (%)	23 (85.10%)	11 (84.61%)	12 (85.71%)	0.935
Dyslipidemia; N (%)	17 (62.96%)	11 (84.61%)	6 (42.86%)	0.025
DM; N (%)	5 (18.50%)	2 (15.38%)	3 (21.43%)	0.686
CAD; N (%)	18 (66.67%)	10 (76.92%)	8 (57.14%)	0.276
Bodyweight, Kg	60.00 (12.35)	60.00 (7.00)	65.15 (12.65)	0.011
BMI, Kg/M^2	23.01 (3.56)	22.22 (2.79)	24.21 (2.95)	0.108
LVEF,%	42.60 (19.00)	45.50 (20.00)	42.20 (19.50)	0.279
Drugs, N (%)				
ASA	23 (85.10%)	11 (84.61%)	12 (85.71%)	0.936
Other antiplatelet	21 (77.78%)	12 (92.31%)	9 (64.29%)	0.080
Atorvastatin	20 (74.07%)	8 (61.54%)	12 (85.71%)	0.152
Other statin	4 (14.80%)	3 (23.07%)	1 (7.14%)	0.244
fibrate/ezetimibe	5 (18.51%)	2 (15.38%)	3 (21.43%)	0.686
B-blocker	22 (81.48%)	11 (84.61%)	11 (78.57%)	0.686
ACEI/ARB	20 (74.07%)	8 (61.54%)	12 (85.71%)	0.152
Diuretics	18 (66.67%)	8 (61.54%)	10 (71.43%)	0.586
DM drugs (oral)	6 (22.22%)	3 (23.07%)	3 (21.43%)	0.918
Insulin	1 (3.70%)	0 (0.00%)	1 (7.14%)	0.691
Lab				
Hemoglobin, g/dl	12.26 ± 1.64	11.68 ± 1.03	12.79 ± 1.90	0.085
FBS, mg/dl	119.77 ± 27.47	112.38 ± 28.69	117.15 ± 25.92	0.644
HbA1C,%	6.93 ± 1.11	6.94 ± 1.07	6.92 ± 1.17	0.975
Baseline serum creatinine, mg/dl	1.43 ± 0.29	1.45 ± 0.28	1.41 ± 0.29	0.744
Baseline eGFR, ml/min/1.73m^2	45.00 (15.50)	44.00 (13.00)	51.00 (14.25)	0.054
CAG details				
Contrast volume, ml	60.00 (110.00)	140.00 (120.00)	40.00 (31.25)	0.007
Mehran risk score	5.00 (6.00)	6.00 (7.00)	4.50 (4.50)	0.080
Total CAG times, minute	53.00 (61.50)	78.00 (63.00)	48.00 (44.50)	0.024
Intravenous fluid, L	1 (0)	1 (0)	1 (0)	0.144

*Plus-minus value is mean ± SD, number with parenthesis are median with interquartile range
Abbreviations: ASA, Aspirin; ACEI/ARB, Angiotensin-Converting-enzyme inhibitors/Angiotensin II receptor blocker; DM, Diabetes Mellitus; BMI, Body Mass index; CAD, Coronary artery disease; CAG, Coronary angiogram; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; g/dl, gram/deciliter; HbA1C, Glycosylated hemoglobin A1C; IQR, Interquartile range Kg, Kilogram; L, Liters; LVEF, Left ventricular ejection fraction; ml, Milliliters; mg/dL, milligrams/deciliter; sd, Standard deviation

Table 2 Primary outcome of CA-AKI in std-group and RIPC group*

Outcomes	Total	Std-group	RIPC	P-value
AKI at 48 hrs, N (%)	2 (7.40%)	2 (15.38%)	0 (0%)	NA
AKI at 1 week, N (%)	1 (3.70%)	1 (7.69%)	0 (0%)	NA
Scr at 48 hrs, mg/dL	1.29 (0.33)	1.29 (0.28)	1.27 (0.35)	0.256
Scr at 1 week, mg/dL	1.34 (0.38)	1.41 (0.56)	1.34 (0.31)	0.148
eGFR at 48 hrs, mg/dL	51.11 ± 12.09	46.69 ± 11.96	55.21 ± 10.68	0.072
eGFR at 1 week, mg/dL	48.44 ± 11.62	43.31 ± 12.02	53.21 ± 8.87	0.027

*Plus-minus value is mean ± SD, number with parenthesis are median with interquartile range
Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; hr, hours; IQR, Interquartile range; mg/dL, milligrams/deciliter; NA, not applicable; Scr, serum creatinine; sd, standard deviation

Table 3 Secondary outcome

Secondary Outcome	Std-group, Incidence	RIPC-group, Incidence
Initiate hemodialysis	0	0
Death	0	0
Adverse event	0	0

DISCUSSION

This study showed no CA-AKI events in the RIPC group. By contrast, a few CA-AKI incidences occurred in the std group at 48 hrs and 1 week. Given the low incidence and small number of participants during the COVID-19 era, statistical analysis was not performed to detect the differences between the two groups. Therefore, the std group had baseline characteristics in the timing of the procedure and amount of contrast more than the RIPC group, which may lead to more CA-AKI events.

A previous systematic review reveals different results in each study, with no definite conclusion[5]. Most studies include patients who proceed in elective schedules with low-to-moderate risk of CA-AKI, which may lead to nonsignificant results of CA-AKI events between the RIPC and standard management[7,13]. However, the study in the CAG emergency setting showed that RIPC may significantly protect CA-AKI in patients with low-to-moderate Mehran's score[16]. Unstable hemodynamic status in acute myocardial infarction can increase CA-AKI risk, which differs from the elective setting in our study. Furthermore, another study used a biological marker, namely, urinary excretion of liver-type fatty acid-binding protein, which reflects tubulointerstitial damage and may early detect CA-AKI than serum creatinine[7]. Compared with our study, using serum creatinine to detect CA-AKI may not detect subclinical tubular injury.

The limitation of the study was the small number of participants, which led to low incidence and the inability to obtain statistical significance. Thus, whether the intervention is effective remains unknown, and it can only be interpreted as a pilot study. Furthermore, most participants had low-to-moderate risk of CA-AKI based on Mehran's risk score.

CONCLUSION

RIPC may be safe to implement in a systematic strategy for the prevention of CA-AKI post-CAG. Therefore, some researchers tend to improve CA-AKI. Further studies using a large number of participants may verify the benefit and provide definite conclusion.

CONFLICT OF INTEREST

None

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ ethical restrictions.

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