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Is there a protective effect with remote ischemic preconditioning on contrast-induced acute renal injury after coronary angiography in low-risk patients?

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ABSTRACT

Background: Contrast-induced acute kidney injury (CIN-AKI) is a serious complication of coronary angiography. Given the weaknesses in the common protective methods used to prevent CIN-AKI, a safe and effective strategy is needed. RIPC has been shown to have a nephroprotective effect.

Objectives: We aimed to determine the protective effect of RIPC on CIN-AKI after angiography or percutaneous coronary intervention (PCI) in low-risk patients.

Patients and Methods: In our study, 140 low-risk patients who needed angiography or PCI, were assigned to either RIPC or control group. In each group, serum creatinine and urinary neutrophil gelatinase-associated lipocalin (uNGAL) were measured before the procedure. Serum creatinine was measured daily for 2 days and uNGAL was measured 6 and 24 hours after the procedure. Diagnosis of AKI was, according to the Kidney Disease; Improving Global Outcomes (KDIGO) criteria (2012).

Results: The mean age in the remote ischemic preconditioning (RIPC) group was 56.8 ± 11.4 years and 56.3 ± 11.8 years in the control group. We observed no significant difference regarding patient's characteristic and renal biomarkers at baseline. There was no significant difference in the incidence of AKI (P = 0.116). The uNGAL increased by 36.2% 6-hour after the procedure in patients with AKI, while at the same time, this biomarker increased only by 4.3% in patients without AKI.

Conclusions: We concluded that RIPC, with 3 cycles of 5-minute ischemia and 5-minute reperfusion, did not decrease CIN-AKI or altering renal biomarkers course in low-risk patients undergoing coronary angiography or PCI. Additionally, uNGAL, seems to be an appropriate biomarker for early diagnosis of CIN-AKI, 6 hours after contrast media exposure.

Original Article

Implication for health policy/practice/research/medical education:
In a study on 140 low-risk patients undergoing coronary angiography or PCI, we found that RIPC, with 3 cycles of 5-minute ischemia and 5-minute reperfusion, did not decrease CIN-AKI (*P*=0.116). Additionally, uNGAL seems to be an appropriate biomarker for early diagnosis of CIN-AKI, 6 hours after contrast media exposure.

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1. Background

Acute kidney injury (AKI) is characterized by a sudden loss of kidney function, resulting in nitrogen retention and other waste products that are normally excreted by the kidneys. Iodine-containing contrast medium used for imaging is one of the major causes of AKI (1). Contrast-induced acute kidney injury (CIN-AKI) is a serious renal complication of coronary artery angiography and is one of

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the leading causes of hospitalization in 12% of cases and has increased in recent decades (2). High mortality rate and morbidity incidence are accompanied by the occurrence of this complication (3).

The most crucial risk factor for the development of CI-AKI is moderate to severe renal dysfunction (glomerular filtration rate; GFR <60 mL/min, Cr >120 mmol/L). Other risk factors include diabetes, decreased left ventricular function, age, concomitant use of other nephrotoxic agents, high volume of contrast medium, hypotension during the procedure, and high or low hematocrit (due to dehydration or anemia) (4,5).

Due to increasing incidence of CIN-AKI, physicians should consider various renoprotective strategies (6). Contrast medium with lower osmolality, hydration protocols, and prophylactic drugs such as statins and ascorbic acid are among the common methods used to prevent this complication (7). Given the weaknesses and the difficulty of these protective methods and the considerable incidence of CIN-AKI despite their usage, a safe, achievable and effective strategy is needed to block this complication (8).

One of the main mechanisms of CIN-AKI seems to be the hypoxia of the renal tubular epithelial cells caused by vasoconstriction and release of reactive oxygen species (ROS). Blood flow return to an organ after an ischemic period leads to some damage to the parenchyma and cause organ dysfunction, which is called reperfusion injury. Ischemic conditioning is an adaptive response to short ischemia that protects organs against long-term outcomes and reperfusion injury, which can be either technical or pharmacological (9). RIPC, which is applied to the upper or lower limbs before receiving contrast medium, has been shown to reduce the mortality rate associated with CIN-AKI. Its effect on renal function is not clear in the long-term and requires further study (4).

AKI is commonly diagnosed by measuring serum creatinine. Unfortunately, serum creatinine is not a perfect predictor for early diagnosis of AKI. Lack of biomarkers that can predict an AKI early led to numerous studies to diagnose and treat this condition at the early stage (10). Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein that naturally can be found with a very low level in human tissues such as the kidneys, lungs, stomach, and colon, and can be induced and measured easily in serum or urine after an epithelial damage. Urine NGAL (uNGAL) is used as an early, sensitive and non-invasive biomarker for AKI in the early stage of this complication (11).

2. Objectives

The aim of this study was to evaluate the role of RIPC of the upper arm on protection from CIN-AKI following coronary angiography or percutaneous coronary intervention (PCI) with stable coronary artery disease and low risk patients for CIN-AKI.

3. Patients and Methods

3.1. Study design and setting

This was a randomized controlled clinical trial study conducted at Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences in 2016 to 2017. It investigates the effect of RIPC upon AKI in patients receiving coronary angiography or PCI. The study design is shown in Figure 1.

3.2. Participants

Eligible patients were those with stable coronary artery disease needed coronary angiography and PCI. The history, demographic information and informed consent were taken from all patients.

The inclusion criteria were;

1. Age equal to or greater than eighteen years
2. Hospitalized patients requiring angiography or PCI
3. Patients who have consent to participate in the study
4. Patients who do not use nephrotoxic drugs 72 hours before angiography or PCI
5. Patients who do not have proteinuria

The exclusion criteria were;

1. Patients with renal dysfunction (GFR <60 mL/min) based on Kidney Disease Improving Global Outcomes (KDIGO) criteria
2. Pregnant women
3. Patients needing an emergency angiography or PCI
4. Patients with cardiogenic shock or recent cardiac infarction

Around140 patients who fulfilled the previously mentioned criteria were included in the study.

3.3. Intervention

Before performing the procedure, patients estimated glomerular filtration rate (eGFR) was determined using CKD-EPI equation (Chronic Kidney Disease Epidemiology Collaboration). Eligible patients were randomized to the remote ischemic post-conditioning (RIPC) treatment group or the control group (randomization was done by random allocation software). Around 70 individuals were in the treatment group and 70 were in the control group. All eligible patients were prepared with a limb cuff wrapped around the upper arm one hour before the procedure. In the treatment group, RIPC was performed via the automated delivery of three cycles of 200 mm Hg blood pressure cuff inflation for five minutes followed by cuff deflation for five minutes. In the control group, sham-RIPC intervention was induced by three cycles of upper-limb pseudo ischemia (low pressure: five minutes blood pressure cuff inflation to a pressure of 20 mmHg and five minutes cuff deflation). Afterward, all patients were treated with coronary angiography or PCI by one cardiac interventionist who was unaware of patient randomization.

All patients received standard of care, according to established clinical practice guidelines. At least 6 hours before angiography or PCI, patients received 300 mg of

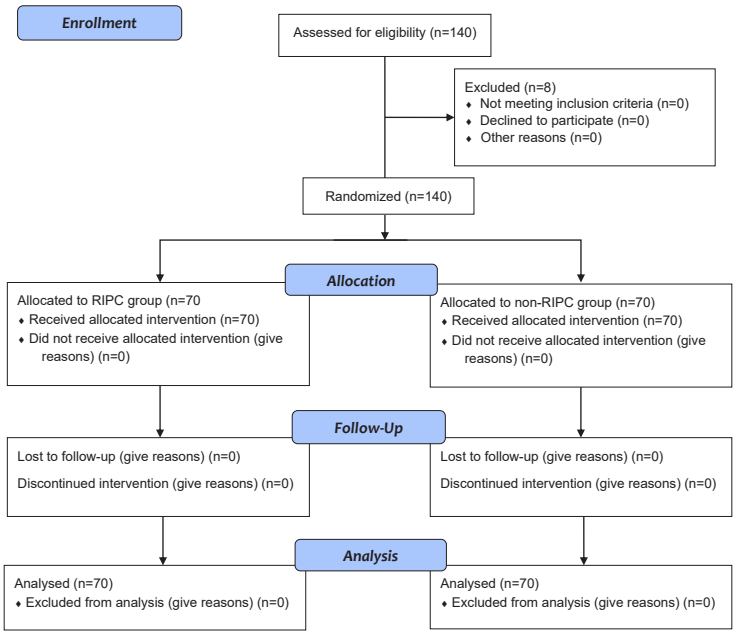

Figure 1. CONSORT flow diagram of the study.

aspirin and 300 mg of clopidogrel. No other drugs such as angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARB) statins and diuretics were discontinued 24 hours before procedure. Moreover, they received heparin (100-70 units/kg) to reach the time of blood clotting for more than 250 seconds. The low-osmolality contrast medium was used and its volume was calculated based on the patient's weight. The hydration plan included normal saline solution one mL/kg of body weight per hour for 12 hours before the procedure and 24 hours after it.

3.4. Study endpoints

Before the procedure, the serum and urine samples were taken to evaluate the serum creatinine (Cr) and uNGAL, then serum creatinine was measured daily, for 2 days and urine specimen was taken to evaluate uNGAL at 6 and 24 hours after the procedure. Serum creatinine and uNGAL were measured by an auto-analyzer and human NGAL ELISA kit (Hu-266, Eastbiopharm company, Hangzhou, China) respectively.

The primary study endpoint was AKI, defined by the 2012 KDIGO criteria (12). KDIGO criteria define AKI as any of the following;

- Increase in serum creatinine by 0.3 mg/dL or more within 48 hours or
- Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or
- Urine output less than 0.5 mL/kg/h for 6 hours.

Secondary endpoints were the relative changes in serum creatinine at 24 and 48 hours and uNGAL at 6 and 24 hours after the procedure compared to baseline.

3.5. Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the ethical committee of Hormozgan University of Medical Sciences (ethical code; HUMS.REC.1396.43). This paper is a part of thesis of Sanaz Soleymani, in department of internal medicine of Hormozgan University of Medical Sciences. Besides that, the study protocol was registered as in the Iranian registry of clinical trials (identifier: IRCT201808200408338N1;https://www.irct.ir/trial/33756).

3.6. Statistical analysis

Statistical analysis was performed by SPSS software V22, SPSS Inc., Chicago, IL, USA. The Kolmogorov-Smirnov test was used to determine data distribution. The t-test was used for the continuous variables that conformed to a normal distribution. The Mann–Whitney U test was used for continuous variables that did not conform to a normal distribution. Crosstabs and Chi-square test were performed for categorical variables. The significance level was considered to be less than 0.05.

4. Results

4.1. Patients' characteristics

A total of 140 patients were enrolled in the study of which 70 were in treatment (RIPC) group and 70 were in case (sham RIPC) group. We observed no significant difference between the two group regarding age, gender, smoking, diabetes, contrast volume/kg, hematocrit and eGFR (Table 1). The mean age was 56.3 ± 11.8 years in RIPC group and 56.8 ± 11.4 years in sham RIPC group (Table 1).

Patients' clinical characteristics are presented in Table 1.

Of 140 patients, 79 were male and 61 were female. In RIPC group, 41 (58.6%) were male and 29 (41.4%) were female and in the control group, 38 (54.3%) were male and 32 (45.7%) were female. In RIPC group there was 23 smoker and 47 non-smokers and in the control group, the number of smokers and non-smoker were 20 and 50, respectively. In the control group, 17 patients (24.3%) were known case of diabetes mellitus (DM), and 13 patients (18.6%) were DM positive in RIPC group. In female patients, mean hematocrit in RIPC and control group was 39.2 ± 3.7 and 38.2 ± 3.6, respectively. In our two studied groups, male patient's hematocrit was 46.0 ± 3.9% and 43.9 ± 3.8%, respectively. Estimated GFR was 77.76 ± 15.29 cc/min in the control group and 79.25 ± 16.38 cc/min in the RIPC group.

4.2. Clinical results

The overall incidence of AKI was 7.8% (11/140). Of 11 patients, 8 were in the RIPC group and 3 were in the control group. As we observed, the occurrence of CIN-AKI was higher in the RIPC group with no significant difference (P = 0.116; Table 2).

There were no significant differences in serum creatinine between the two groups before the procedure. 24-hour and 48-hour serum creatinine were higher in the RIPC group (Table 3), but we observed no significant differences between the two groups regarding serum creatinine in the study periods. In both groups, serum creatinine had an ascending course, which was statistically significant (P<0.001).

According to Table 3, uNGAL was lower in RIPC group, before the procedure, 6-hour and 24-hour after, but the interaction effect of time and group was not statistically significant on this biomarker (P=0.116).

In our study, in patients with CIN-AKI, 24-hour and 48-hour serum creatinine increased by 28.5% and 40.4%, respectively (compared to baseline of 1.08 mg/dL and 1.18 mg/dL compared to 0.84 mg/dL), while in other patients, serum creatinine increased 6.1% and 8.1%, in 24 and 48 hours after the procedure, respectively (1.04 mg/dL and 1.06 mg/dL compared to 0.98 mg/dL) (Figure 2).

In 11 patients with CIN-AKI, uNGAL evaluation demonstrated a significant increase over the first 6 hours, reaching 36.2% of the baseline (from 489.1 ng/mL to 663.3 ng/mL). While at the same time, in patients without CIN-AKI, it increased by 4.3% (517.6 ng/mL to 539.9 ng/mL). We noted that uNGAL decreased 24 hours after the procedure compared to previous 6-hour measurement in both groups (547.3 ng/mL in CIN-AKI group and 524.8

Table 1. Clinical characteristics of patients

	RIC		*P* value
	No RIPC	RIPC	
Sex			
Female	32 (45.7%)	29 (41.4%)	0.609
Male	38 (54.3%)	41 (58.6%)	
Age	56.8 ± 11.4	56.3 ± 11.8	0.720
Smoking	20 (28.6%)	23 (32.9%)	0.583
DM	17 (24.3%)	13 (18.6%)	0.410
Hematocrit			
Female	38.2 ± 3.6	39.2 ± 3.7	0.529
Male	43.9 ± 3.8	46.0 ± 3.9	0.290
Contrast volume/kg	0.644 ± .506	0.614 ± .400	0.374
Baseline Cr	0.98 ± .20	0.97 ± .20	0.569
Baseline eGFR	77.76 ± 15.29	79.25 ± 16.38	0.569
Baseline uNGAL	562.9 ± 145.6	467.8 ± 167.8	<0.001

Table 2. AKI occurrence by KIDIGO criteria

	RIC				*P* value
	No RIPC		RIPC		
	No.	%	No.	%	
AKI					
No	67	95.7	62	88.6	0.116
Yes	3	4.3	8	11.4	

Table 3. Serum creatinine and uNGAL changes

	RIC		*P* value
	No RIPC	RIPC	
Cr24	1.04 ± 0.20	1.05 ± 0.16	0.604
Cr48	1.05 ± 0.20	1.09 ± 0.16	0.252
NGAL6	589.9 ± 159.1	509.7 ± 190.2	0.008
NGAL24	575.3 ± 135.0	477.7 ± 159.3	<0.001

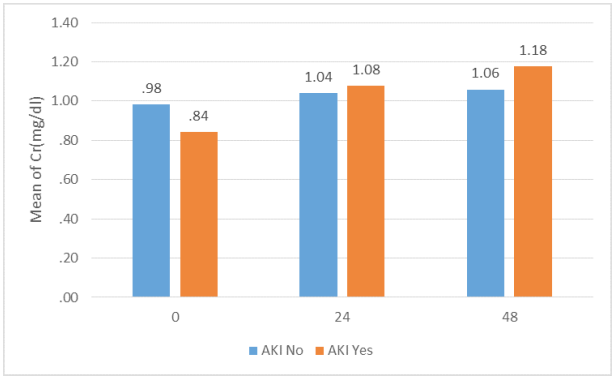

Figure 2. Comparison of serum creatinine in patients with and without AKI.

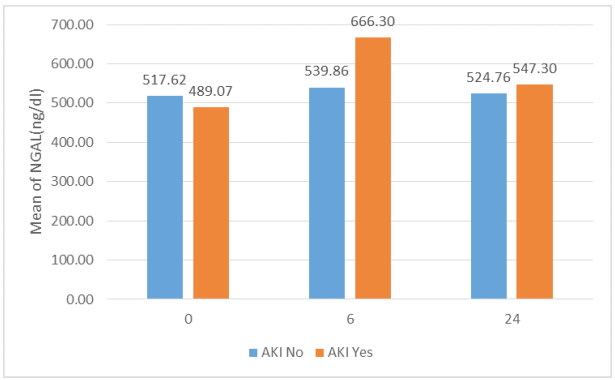

Figure 3. Comparison of uNGAL in patients with and without AKI.

ng/mL in no CIN-AKI group) (Figure 3).

Figure 4 demonstrates the uNGAL changes in RIPC and no RIPC group in patients who were diagnosed with AKI. In Figures 5 and 6, serum creatinine value and uNGAL course are explained in AKI and no AKI patients in the RIPC group.

5. Discussion

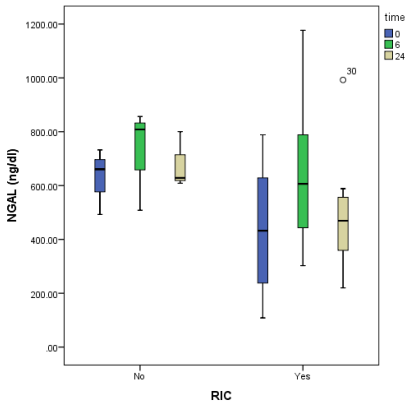

Figure 4. Comparison of uNGAL course in patients with AKI in RIPC and no RIPC groups.

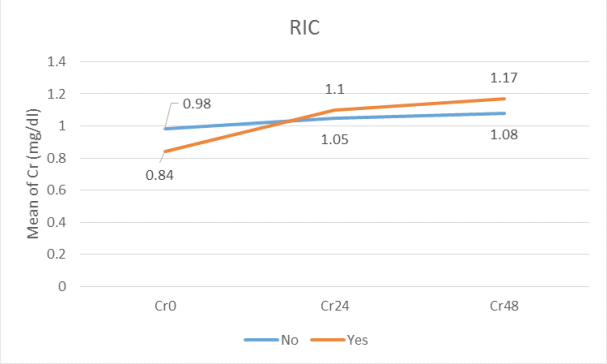

Figure 5. Comparison of serum creatinine course in patients with and without AKI in RIPC group.

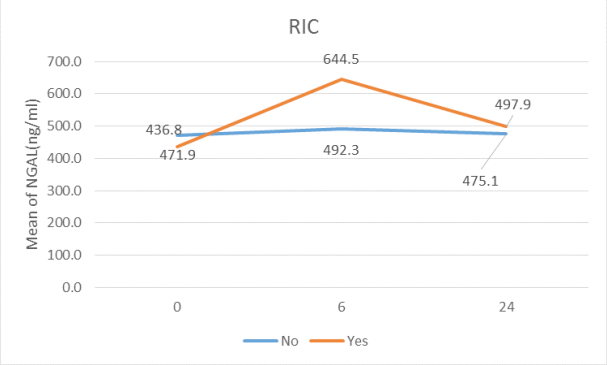

Figure 6. Comparison of uNGAL course in patients with and without AKI in RIPC group.

Due to the widespread use of contrast medium, CIN-AKI has become the third leading cause of renal failure (13). It is one of the most common renal complications after PCI and coronary artery angiography (14). The incidence of CIN-AKI varies from 2% in the general population to more than 50% in high-risk groups (15). Using contrast medium with low osmolality, hydration protocols, and prophylactic drugs are among the methods used to prevent this complication (7). However, due to the difficulty of these methods and the considerable occurrence of CIN-AKI despite using preventive strategies, a safe, feasible and effective method is needed to prevent this complication (8).

Remote ischemic conditioning (RIC) is a non-pharmacological method that involves various cycles of transient non-lethal ischemia (16). This method includes RIPC and remote ischemic post-conditioning (RIPost) (17). It has been shown that RIC has a nephroprotective role in patients undergoing renal or non-renal surgeries (18). Several meta-analyses supported the renal protective role of RIPC in recent years (8,17,19). Zhou et al showed that RIC, whether RIPC or RIPost, could efficiently exert a renoprotective impact in intravascular contrast administration and diminish the incidence of relevant adverse consequences (8). According to a meta-analysis conducted by Li et al, RIPC can reduce the postoperative occurrence of AKI in cardiac and vascular surgery patients (19). In the study by Bei et al, pool data analysis demonstrated that RIC reduced the incidence of CIN-AKI in those receiving PCI or coronary angiography (17).

The principal finding of our study was that RIPC did not decrease the occurrence of CIN-AKI or alter renal biomarker course after PCI or coronary angiography.

RIPC is commonly induced by three or four cycles of ischemia and reperfusion. We used three cycles of 5-minute ischemia and 5-minute reperfusion protocol applied to the upper extremity.

In the study of Zhou et al, the subgroup analysis revealed that 4 cycle protocol was significantly effective in renal protection whereas, 3 cycle protocol was not (8). Accordingly, Dong et al (20) and Lu et al (21) established the relation between conditioning cycles and its effectiveness and noted that more cycles result in a more potent RIC. In the study by Bei et al (17), pooled results showed that RIC of the upper arm had significantly reduced the risk of CIN-AKI, but RIC of the lower limb in patients undergoing PCI or coronary angiography did not have the same effect. Moreover, in the studies of Er et al (2) and Igarashi et al (22), results showed that RIPC with the 4-cycle protocol, prevents CIN-AKI after elective coronary angiography in high risk and low-moderate risk patients, respectively. On the contrary, Pederson et al (23) and Menting et al (24) suggested that RIPC leads to little or no difference in the incidence of AKI, similar to our study. In the former study, RIPC, when applied with 4 cycle protocol, was not associated with a decrease in acute renal

dysfunction occurrence or improvement in either of the renal biomarkers (plasma Cr, eGFR, plasma cystatin C and plasma and urine NGAL)s in pediatric patients (0-15 years old) undergoing a congenital heart defect surgery. The later was a Cochrane review, noted that the available data do not confirm the efficacy of RIPC in reducing renal ischemia-reperfusion injury in patients undergoing major cardiac and vascular surgery in which renal ischemia-reperfusion injury may occur, with moderate-high certainty evidence.

Zarbock et al (25) used 3 cycle protocol to determine the effect of RIPC in patients undergoing cardiac surgery. They noted that RIPC significantly reduced the occurrence of acute renal dysfunction in high-risk patients. Contrary to our study which failed to demonstrate renal protection with RIPC in low-risk patients. In comparison, we excluded patients with renal dysfunction (GFR <60 mL/min), but only patients with a high risk of renal dysfunction were enrolled in the study by Zarbock et al. Two consensus conferences concluded that high-risk patient population would be most likely to benefit from RIPC (26). Additionally, we studied CIN-AKI after PCI or coronary angiography, whereas in Zarbock et al study, they focused on patients who had coronary artery bypass surgery. Choi et al (27), also used 3 cycle protocol (3 10-minute cycles of lower limb ischemia and reperfusion) to determine the effect of RIPC during complex valvular heart surgery. They concluded that RIPC did not reduce the degree of renal injury or incidence of AKI.

In addition to using the 4-cycle protocol, some studies emphasized some additional strategies to enhance RIPC efficiency. Zhou et al (8) noted that sufficient intravenous hydration, conducted before or after contrast administration, might have synergism with RIC and could enhance its efficiency. Additionally, RIC was considerably efficient when used with low and medium dose contrast. Additionally, conditioning with the arm lessened the risk of CIN-AKI rather than the thigh.

We noted that 24-hour and 48-hour serum creatinine was similar in RIPC and the control group. Additionally, we observed no significant difference in the course of uNGAL. We concluded that RIPC could not alter renal biomarkers after PCI or coronary angiography. In Li et al meta-analysis (19), no differences in the changes in AKI biomarkers between RIPC and control groups in patients undergoing cardiac and vascular interventions was seen. Yang et al (28) noted that RIPC decreased the risk of AKI in patients undergoing cardiac and vascular interventions compared with control group, but there were no differences in levels of postoperative kidney biomarkers (serum creatinine and GFR between two groups). Neutrophil gelatinase-associated lipocalin was reported in several trials. Three trials did not report a significant difference in postoperative urine or plasma NGAL levels between the RIPC intervention and control groups (23,27,29) whereas one trial reported that RIPC significantly decreased urine NGAL levels 24 and 48 hours after surgery (2).

AKI is commonly identified by determining serum creatinine. In recent years, a greater understanding of AKI led to changes in the KDIGO diagnostic criterion, which less increase in serum creatinine (0.3 mg/dL) is considered for diagnosis (12). However, due to characteristics of serum creatinine, this biomarker has a limited role in the early AKI detection (30). Therefore, it requires to use other biomarkers for detecting AKI in its early stage (31).

Neutrophil gelatinase-associated lipocalin (NGAL) has been considered as a promising biomarker for the early diagnosis of AKI (32). Neutrophil gelatinase-associated lipocalin is expressed at very low levels in the kidney (33). It is markedly increased in stimulated epithelia, and it is also one of the maximally expressed genes in the kidney after early ischemic injury (34). Studies have shown that NGAL has the ability to detect AKI in the first 4-8 hours in adult patients that is much earlier than the time needed to diagnose with serum creatinine, which requires at least 24 hours (35,36).

The measurement of uNGAL is a good biomarker for the early diagnosis of AKI with various diagnostic features, such as intravenous contrast injection (37). This biomarker has been widely studied in recent years and has been proven to have a high sensitivity and specificity in the detection of AKI (38). Using uNGAL for the diagnosis of acute renal dysfunction also reduces the cost of treatment, especially if it's combined with serum creatinine. (39).

Our result showed that uNGAL increased significantly in patients with CIN-AKI 6 hour after the procedure and could be considered as an acceptable biomarker in early diagnosis of CIN-AKI. Ling et al (37) noted that NGAL showed a good performance in early diagnosis of CIN-AKI as compared with serum creatinine after coronary angiography. On the basis of uNGAL levels, CIN-AKI could be diagnosed at least 24 hours earlier than by serum creatinine.

In the study by Ribitsch et al (40), uNGAL failed to predict CIN-AKI in patients with chronic kidney disease (CKD). In this study, uNGAL specificity and sensitivity for the diagnosis of CIN-AKI were 80% and 28%, respectively. In some other studies, it was demonstrated that uNGAL values were not different among patients with and without acute renal dysfunction up to 24 hours after surgery (cardiac surgery and angiography, respectively) in case of preoperative eGFR <60 mL/min (41,42). In another study evaluating patients with eGFR <30 mL/min, it was concluded that although NGAL seemed to be a reliable marker for CIN-AKI diagnosis, it had a poor positive predictive value 6 hours after receiving contrast media (43). The main conclusion from above-mentioned studies is that in patients with chronic renal dysfunction, uNGAL seem to lack the diagnostic power to provide specialists with an early intervention strategy to prevent further renal damage and dysfunction following the contrast media

administration(40).

The findings of this study must be interpreted in view of its limitations. The main limitation was the relatively small sample size. Kidney function was assessed just by some short-term outcomes without a long-term follow-up. Further studies with larger sample size accompany with the long-term renal function and patients' morbidity evaluation could fully assess the protective role of RIPC in contrast-induced nephropathy.

6. Conclusions

Our study showed that RIPC, with 3 cycles of 5-minute ischemia and 5-minute reperfusion, did not decrease CIN-AKI or alter renal biomarkers course in patients undergoing coronary angiography or PCI. Additionally, uNGAL, seems to be an appropriate biomarker for early diagnosis of CIN-AKI in patients without CKD, 6 hours after contrast media exposure.

Study limitations

The relatively small sample is a limitation of our investigation. In this study, renal function was analyzed only with short-term markers. Therefore, the reliability of this study should be further confirmed by larger and longer clinical observations.

Authors' contribution

HS designed the study, observed accuracy and validity of the study. SS collected the data and follow the study. MA analyzed data. MT supervised the project. SS wrote the paper. All authors edited and revised the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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