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Original Article

Evaluation of the efficacy of ischemic post-conditioning for the improvement of contrast induced nephropathy on patients with acute coronary syndrome

Jinzhu Zhang, Xiaoyan Lin, Baoqing Tian, Chunmei Liu

Department of Cardiovascular Medicine, Linyi Central Hospital, Linyi 276400, Shandong Province, China

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Abstract: Objective: In order to evaluate the efficacy of ischemic post-conditioning (IPTC) for the contrast induced nephropathy on patients with acute coronary syndrome. Methods: One-hundred and ninety-four patients with acute coronary syndrome and percutaneous coronary intervention (PCI) were enrolled and analyzed retrospectively. Depending on whether or not performing IPTC, the patients were divided into control group (101 cases) and IPTC group (93 cases). In the control group, PCI was used directly for the patients. Whereas in the IPTC group, IPTC method was employed firstly as follows: 1 minute after the reconnection of infarcted coronary artery, the balloon was inflated and deflated repeatedly at the occluded area under low pressure for 3 times. Then the PCI was performed on the patients. The clinical baseline data, renal function index, incidences of contrast induced nephropathy and major adverse cardiovascular events were recorded and compared. Results: There was no significant difference on basic clinical information (including gender, age, body mass index, clinical disease, number of coronary lesion vessels, dosage of contrast agent and left ventricular ejection fraction) between two groups (all $P>0.05$). For the serum creatinine (Scr), cystatin C (CysC), estimated glomerular filtration rate (eGFR) and urine neutrophil gelatinase associated lipocalin (NGAL) levels before the surgery, there were also no significant differences between two groups (all $P>0.05$). Forty-eight hours after the surgery, the levels of Scr, CysC and NGAL in IPTC group were all significantly lower than that in control group (all $P<0.05$). There was significantly higher eGFR level in IPTC group than that in control group ($P<0.05$). For the incidences of contrast induced nephropathy and major adverse cardiovascular events, there were significantly lower rates in IPTC group (5.38% and 7.53%, respectively) than that in control group (21.78% and 30.69% respectively, both $P<0.05$). Conclusion: IPTC could promote the protection on renal function for the patients with acute coronary syndrome and PCI treatment, decrease the incidence of contrast induced nephropathy, and played a positive role in prognosis improvement. This approach deserves more researches and applications in the future.

Keywords: Acute coronary syndrome, percutaneous coronary intervention, ischemic post-conditioning, contrast induced nephropathy

Introduction

As a serious cardiovascular disease, acute coronary syndrome is a clinical syndrome with different stages of occlusive thrombus, which induced by instable coronary atherosclerotic plaque, and often occurs in middle and old age people with underlying diseases [1]. In recent years, percutaneous coronary intervention (PCI) was widely employed in the treatment of acute coronary syndrome. This method could reconnect the coronary artery, improve the myocardial perfusion, and relieve the symptoms with exact efficacy. At meanwhile, the incidence of contrast agent related complications was increased recently. Due to significant difference in constitution and clinical features of patients with acute coronary syndrome, the contrast induced nephropathy were appeared with different stages after the PCI treatment. Moreover, it could induce the acute renal failure on patients eventually.

The contrast induced nephropathy was treated as the main influence factor for the short and long-term efficacy of PCI. The contrast induced nephropathy was mainly caused by coronary angiography, and the pathogenesis has not fully elucidated yet. The prevention of contrast induced nephropathy got more attention in clini-

cal applications now. For the prevention methods for the contrast induced nephropathy, the hydration treatment, optimization of different types of contrast agents, and application of cysteine were used in the previous studies [2, 3]. However, the incidence of contrast induced nephropathy was still high. It was necessary to find a clear and effective preventive approach for the contrast induced nephropathy. In a recent report, the occurrence and development of contrast induced nephropathy may be closely related to the renal ischemia reperfusion injury [4]. This result provided the evidence for the ischemic post-conditioning (IPTC) method on the protection of renal function. However, the protective effects of IPTC for renal function were mainly limited on animal studies. The clinical studies for this were still less. Moreover, there was no conclusion for reducing contrast induced nephropathy by IPTC till now.

Thus, the efficacy of IPTC for the improvement of contrast induced nephropathy on patients with acute coronary syndrome was evaluated in this study.

Materials and methods

Patient information

One-hundred and ninety-four patients with acute coronary syndrome and PCI treatment were enrolled and analyzed retrospectively in Linyi Central Hospital from May 2015 to May 2016. Depending on whether or not performing IPTC, the patients were divided into control group (101 cases) and IPTC group (93 cases). In the control group, PCI was used directly for the patients; whereas in the IPTC group, IPTC method was employed before PCI. The inclusion criteria were consisted of (A) meeting the pathology diagnostic criteria for acute coronary syndrome, (B) the onset of disease was shorter than 12 h, (C) performing PCI treatment, (D) grade 0 on thrombolysis in myocardial infarction (TIMI). The exclusion criteria consisted of (A) grade 1-3 on TIMI, (B) formation of collateral circulation, (C) history of acute coronary syndrome and treatment of coronary artery, (C) coagulant function abnormality, (D) allergic to contrast agent, (E) combination of severe renal and liver dysfunction or malignant tumor. The patients understood and signed the informed consent. This study has got approval from local ethical committee.

Treatment program

The PCI was performed in both groups, and described as follows. After the coronary angiography examination through femoral or radial artery, the left and right coronary angiograms in different positions were collected. The sizes of main and branch blood vessels were measured and quantified. Before the operation, aspirin, porlivy, statin drugs and hypoglycemic agents were used on the patients respectively. Heparin (100 U/kg) was employed during the surgery. If the operation was longer than 2 h, additional heparin was needed. The stent implantation was performed for the main vessel of coronary artery. Moreover, the stent implantation could also be used for the branch vessels of coronary artery if necessary. After the surgery, antiplatelet therapy was enhanced. The anti-hyperlipidemia, anti-hypertension, and anticoagulant therapies were given actively for the patients. In the control group, PCI was used directly for the patients. Whereas in the IPTC group, IPTC method was employed: 1 minute after the reconnection of infarcted coronary artery, the balloon was inflated and deflated repeatedly at the occluded area under low pressure for 3 times (continuous one minute for each ischemia or reperfusion). Then the PCI was performed on the patients.

Outcome measures and endpoint events

For all patients, 4 mL blood from cubital vein was collected 12 h before surgery and 48 h after surgery respectively, to determine the renal outcome, including serum creatinine (Scr), cystatin C (CysC), estimated glomerular filtration rate (eGFR) and urine neutrophil gelatinase associated lipocalin (NGAL) levels. The Scr level was measured by ammonia iminohydrolase method. The CysC and urine NGAL levels were determined through enzyme-linked immunosorbent assay. The eGFR was estimated by the diet modified equation of renal disease.

The major endpoint event was the occurrence of contrast induced nephropathy. The judgement standard was performed as follows: the Scr level in 48 h after surgery was increased 25% than that before using contrast agent, or above 44.2 μmol/L. The secondary endpoint event was the occurrence of major adverse cardiovascular events, including arrhythmia, recur-

Table 1. Comparison of clinical baseline data between two groups

Item	Control group (n=101)	IPTC group (n=93)	t/X^2	P
Male (n, %)	63 (62.38)	58 (62.37)	0.745	0.586
Age	58.29±0.35	59.26±0.41	0.415	0.745
Body mass index (kg/m^2)	25.34±4.13	25.23±3.98	0.541	0.671
Clinical diseases (n, %)				
Hyperlipidemia	30 (29.70)	28 (30.11)	0.625	0.632
Hypertension	52 (51.49)	46 (49.46)	0.952	0.452
Diabetes	44 (43.56)	42 (45.16)	0.714	0.547
Coronary heart disease	72 (71.29)	68 (73.12)	0.763	0.516
Coronary lesion vessels (n)			1.239	0.095
One vessel	33	28		
Two vessels	41	41		
Three vessels	27	24		
Dose of contrast agent (mL)	117.54±43.67	121.32±39.76	1.245	0.124
Left ventricular ejection fraction (%)	58.00±8.40	59.00±9.10	1.044	0.145

Note: IPTC, ischemic post-conditioning.

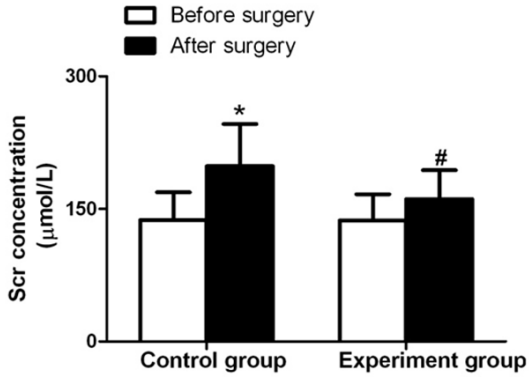

Figure 1. Comparison of Scr level before and after surgery between two groups. There was significant difference on Scr level before and after surgery within control group (*t=2.402, P=0.032). There was significant lower Scr level in IPTC group than that in control group ($^\#$t=2.232, P=0.040). Experiment group: IPTC group. Scr: serum creatinine; IPTC: ischemic post-conditioning.

rence of angina pectoris, cardiac failure, and cardiogenic shock, etc. The patients were followed-up continuously every three months for one year. Then the major adverse cardiovascular events were recorded and analyzed [5, 6].

Statistical analysis

SPSS 18.0 was used for data analysis. The measurement data with normal distribution and homogeneity of variance were expressed by mean ± standard deviation ($\bar{x}$ ± sd). The comparison between groups was conducted with t test. The measurement data without normal distribution were expressed by M (Q1, Q3). The comparison between groups was conducted with Mann-Whitney U test. The counting data was expressed by percentage, and tested by χ^2. The ranked data was tested by rank-sum method. P<0.05 indicated statistically significant difference.

Results

Comparison of clinical baseline data between two groups

There was no significant difference on basic clinical information (including gender, age, body mass index, clinical disease, number of coronary lesion vessels, dosage of contrast agent and left ventricular ejection fraction) between two groups (all P>0.05, **Table 1**).

Comparison of Scr, CysC, eGFR and NGAL levels before and after surgery between two groups

For the Scr, CysC, eGFR and NGAL levels before the surgery, there were also no significant differences between two groups (all P>0.05). Forty-eight hours after the surgery, the levels of Scr, CysC and NGAL in IPTC group were all significantly lower than that in control group (all P<0.05). There was significantly higher eGFR level in IPTC group than that in control group (P<0.05). The data is shown in **Figures 1**-**4**.

Comparison of incidences of contrast induced nephropathy and major adverse cardiovascular events between two groups

For the incidences of contrast induced nephropathy and major adverse cardiovascular events, there were significantly lower rates in IPTC

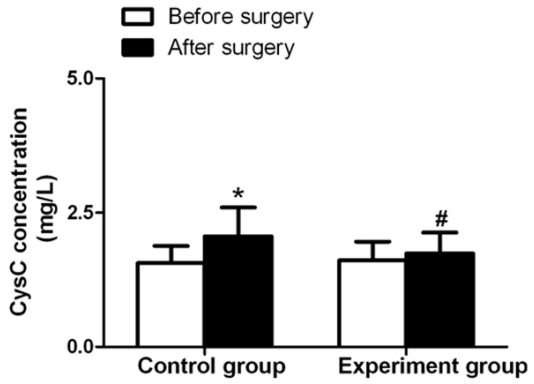

Figure 2. Comparison of CysC level before and after surgery between two groups. There was significant difference on CysC level before and after surgery within control group (*t=2.759, P=0.014). There was significant lower CysC level in IPTC group than that in control group (#t=2.340, P=0.033). Experiment group: IPTC group. CysC: cystatin C; IPTC: ischemic post-conditioning.

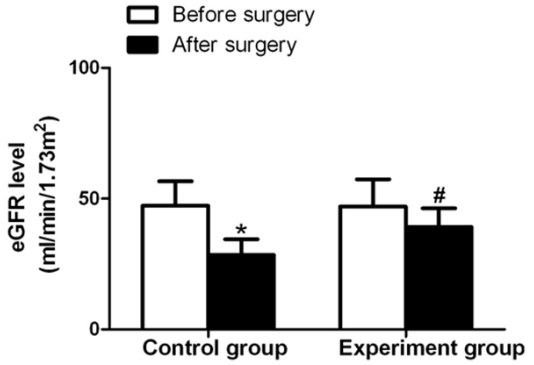

Figure 3. Comparison of eGFR level before and after surgery between two groups. There was significant difference on eGFR level before and after surgery within control group (*t=2.931, P=0.043). There was significant higher eGFR level in IPTC group than that in control group (#t=3.142, P=0.010). Experiment group: IPTC group. eGFR: estimated glomerular filtration rate; IPTC: ischemic post-conditioning.

group (5.38% and 7.53%, respectively) than that in control group (21.78% and 30.69% respectively, χ^2=10.877, P=0.001; χ^2=16.497, P<0.001, **Figure 5**, **Table 2**).

Discussion

The contrast induced nephropathy has already become the most common and serious complications after PCI treatment on patients with acute coronary syndrome. The occurrence of contrast induced nephropathy would increase the difficulty of treatment, and affect the prognosis greatly. There were different stages of abnormity in hemodynamics, and renal ischemic damage in the patients with acute coronary syndrome. After the application of contrast agent, the contrast has the direct toxicity for the renal tubular epithelial cells, and then leads to the occurrence of contrast induced nephropathy in patients eventually. According to the previous studies, the pathological basis of contrast induced nephropathy was renal ischemic

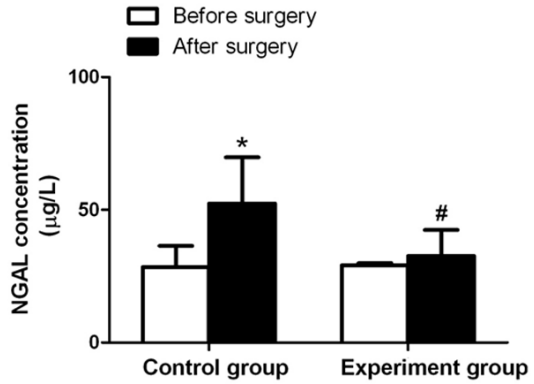

Figure 4. Comparison of NGAL level before and after surgery between two groups. There was significant difference on NGAL level before and after surgery within control group (*t=3.418, P=0.007). There was significant lower NGAL level in IPTC group than that in control group (#t=4.008, P=0.001). Experiment group: IPTC group. NGAL: urine neutrophil gelatinase associated lipocalin; IPTC: ischemic post-conditioning.

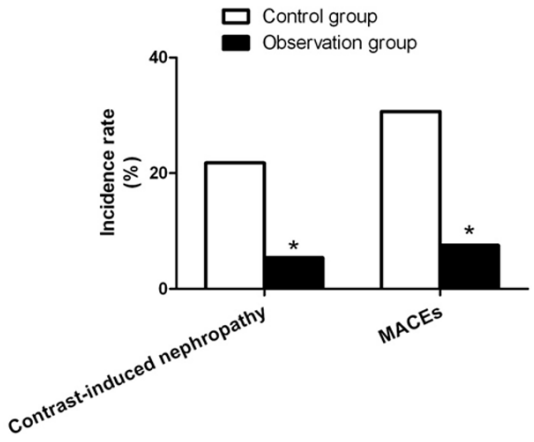

Figure 5. Comparison of incidences of contrast induced nephropathy and major adverse cardiovascular events between two groups. There were significant lower incidences of contrast induced nephropathy and major adverse cardiovascular events in IPTC group than that in control group (*P<0.05). Observation group: IPTC group; IPTC: ischemic post-conditioning.

Table 2. Comparison of incidences of contrast induced nephropathy and major adverse cardiovascular events between two groups (n)

Item	Control group	IPTC group	t/χ^2	P
Cases	101	93		
Contrast induced nephropathy	22	5	10.877	0.001
Major adverse cardiovascular events				
Arrhythmia	8	2	2.223	0.136
Recurrence of angina pectoris	10	3	2.446	0.116
Cardiac failure	6	1	2.045	0.153
Cardiogenic shock	7	1	2.848	0.091

Note: IPTC, ischemic post-conditioning.

injury, whereas the direct reason of contrast induced nephropathy was the cytotoxicity of contrast agent [7-9]. In recent years, with the continuous development of medical technology, the cytotoxicity of contrast agent was decreased. It played a certain role for the reducing contrast induced nephropathy. However, the incidence of contrast induced nephropathy further is still high. In the previous study by Naghavi, there was significantly higher risk on occurrence of contrast induced nephropathy in patients who had incomplete basal renal function [10]. Ye also reported that, the occurrence of contrast induced nephropathy was closely related to the major adverse cardiovascular events, including arrhythmia, recurrence of angina pectoris and cardiac failure, etc. [11]. In this study, the patients with acute coronary syndrome and PCI treatment were defined as the high-risk population for contrast induced nephropathy. The appropriate approaches were needed to prevent the occurrence of contrast induced nephropathy.

For the IPTC, it has already been shown to be one of the treatments for the renal ischemia reperfusion injury. Lagos-Arevalo reported that, the IPTC could significantly decrease the incidence of contrast induced nephropathy after PCI treatment for the patients with acute coronary syndrome [12]. In this study, there were significantly lower rates in IPTC group (5.38% and 7.53%, respectively) than that in control group (21.78% and 30.69% respectively, χ^2= 10.877, P=0.001; χ^2=16.497, P<0.001, **Figure 5**) for the incidences of contrast induced nephropathy and major adverse reaction for cardiovascular. The results indicated that, IPTC could alleviate the ischemia reperfusion injury, protect renal function, decrease the incidences of contrast induced nephropathy and major adverse reaction on cardiovascular, and improve the prognosis.

As a promising treatment for the renal ischemia reperfusion injury, the IPTC was employed one minute after reconnection of infarcted coronary artery. Then the balloon was inflated and deflated repeatedly at the occluded area under low pressure for 3 times. Then the PCI was performed on the patients. Those approaches could help reducing the reperfusion injury. Xu reported that the more than 35% of infarcted area was reduced after the employment of IPTC for the patients with acute coronary syndrome and PCI treatment [13]. Igarashi reported that IPTC showed clearly protection for the heart [14]. Moreover, as a safe and reliable treatment, the IPTC could significantly decrease the incidence of major adverse cardiovascular events. Also, there were several animal studies for the IPTC treatment [15-17]. Those researches showed that the IPTC could significantly improve the prognosis of rats with acute coronary syndrome and renal ischemia reperfusion injury, and protect the myocardium in those animal models [15-17]. According to those studies, the IPTC showed positive effects for the alleviation of ischemia reperfusion injury, and then protect heart and renal functions. In this study, the PCI was directly employed in control group, whereas IPTC was performed first in IPTC group. The results showed that the incidence of major adverse cardiovascular events in IPTC group was significantly lower than that in control group. The efficacy of IPTC on contrast induced nephropathy was also evaluated in this study. The results showed that the incidence of contrast induced nephropathy in IPTC group was significantly lower than that in control group. The reasons were closely related to the alleviation of ischemia reperfusion injury after IPTC treatment, the releasing of humoral factors (including adenosine, bradykinin, etc.), and then the protection for renal. Moreover, the renal was protected through the humoral factors releasing. Based on the previous studies, the remote ischemic preconditioning (RIPC) showed clear protection for the renal. The reasons were the activation of the protection on renal tubular epithelial cells in signal transduction pathways (such as PKC, etc.) after

RIPC treatment, and then decreasing the renal function damage by contrast agent [18-20]. According to the efficacy evaluation in this study, the IPTC showed similar signal transduction pathway with the RIPC, and also improved the protection of renal function in patients with cute coronary syndrome and PCI treatment.

In this study, the preventive effect of IPTC for contrast induced nephropathy was evaluated for the patient with acute coronary syndrome and PCI treatment. As the observation index of renal function judgement, the Scr, CysC, eGFR, and NGAL levels could reflect the real status of renal function exactly, and enhance the determination of renal function synergistically. There were no significant differences on the general information and renal function indexes between two groups before surgery. And on this basis, the levels of Scr, CysC and NGAL in IPTC group were significantly lower than that in control group 48 h after the surgery (all $P<0.05$). There was also significantly higher eGFR level in IPTC group than that in control group ($P<0.05$). Moreover, for the incidences of contrast induced nephropathy, there was significantly lower rates in IPTC group (5.38%) than that in control group (21.78%, $P<0.05$). Those results indicated that IPTC could improve the protection of renal function in patients with acute coronary syndrome and PCI treatment. The possible reasons for reducing incidence of contrast induced nephropathy through IPTC were listed as follows. On the one hand, the IPTC could activate the signal transduction pathway for the protection of renal function, decrease the renal ischemia reperfusion injury, and then reduce the incidence of contrast induced nephropathy. On the other hand, IPTC could alleviate the renal ischemia reperfusion injury, improve heart function, increase renal blood perfusion level timely, and then play a certain role in reducing the incidence of contrast induced nephropathy. In recent years, several studies suggested that large-dose statin drugs in the early stage could decrease the myocardial damage significantly, and also decrease the incidence of contrast induced nephropathy [21-23]. Accordingly, combination of IPTC and statin drugs could improve the protection of heart and renal functions synergistically. This combination therapy was expected to furtherly decrease the incidence of contrast induced nephropathy, but still needs to perform more researches in the future. Meanwhile, the safety of IPTC was relative high. This method could significantly improve the prognosis of patients with acute coronary syndrome, and provide opportunities for the reconstruction of renal blood transportation.

In conclusion, the IPTC could help to protect the renal function in patients with acute coronary syndrome and PCI treatment, decrease the incidence of contrast induced nephropathy, play a positive role in prognosis, and deserve further researches and applications. The less cases, lack of long-term follow-up and efficacy of IPTC data, and retrospective research were limited the results in this study. At the same time, the risk of coronary microembolization may be increased after IPTC, and the patients with grade 1-3 of TIMI whether can be benefited through IPTC are still need to study in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Chunmei Liu, Department of Cardiovascular Medicine, Linyi Central Hospital, No.17 Jiankang Road, Yishui, Linyi 276400, Shandong Province, China. Tel: +86-0539-2251934; E-mail: liuchunmei632c@163.com

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