Effect of Remote Ischemic Preconditioning on the Periprocedural Myocardial Injury Events during Elective Percutaneous Coronary Intervention

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ABSTRACT

Background: Periprocedural myocardial injury (PMI) occurs in at least a third of patients underwent elective percutaneous coronary intervention (PCI). Effect of remote ischemic preconditioning (rIPC) on the PMI and infarction remains elusive. Purpose of this study was to know the effect of rIPC on the PMI and infarction during PCI in patient with coronary artery disease (CAD) underwent elective PCI. **Method**: Forty-two patients with stable coronary artery disease underwent elective PCI were randomized into rIPC group (n= 20) and control group (n=22). RIPC protocol was 4 cycles of inflation-deflation using a blood pressure cuff 20 mmHg above the systolic blood pressure in one of the upper arm. Assessment of PMI was determined by increase of cardiac enzyme CK-MB at 18 to 24 hours post PCI. **Result**: The levels of CK-MB post PCI was significantly lower in the RIPC group than control, 25.15±5.46 vs. 40.59±21.16 µg/mL, respectively (p=0.003). Evidence of PMI was significant lower in the RIPC group than that of the control, 2.3% vs.19.04% (p=0.022), while that of the infarction was not significant difference between both groups, 0% vs. 2 (4.76%), respectively (p=0.489). **Conclusion**: Remote ischemic preconditioning may reduce periprocedural myocardial injury in patient with CAD underwent elective percutaneous coronary intervention.

***Keywords**: Periprocedural myocardial injury, remote ischemic preconditioning, creatine kinase myocardial band, percutaneous coronary intervention.*

It is known that periprocedural myocardial injury (PMI) is a common complication in patient undergoing percutaneous coronary intervention (PCI).[1] The incidence of PMI in patients underwent elective PCI is 15 to 40%.[2,3] PMI is any elevation of creatine kinase myocardial band (CK-MB) above the upper normal limit post PCI.[4] Periprocedural myocardial injury in elective PCI is also correlated with an elevated mortality risk, risk of recurrent infarction and need for revascularization in the future. Although the blood flow at epicardial level is in the range of normal and PCI is considered successful, a disturbance in microcirculation level evidenced by a slight increment in CK-MB level is correlated with a long term cardiovascular prognosis.[5-7]

There are several strategies to avoid a periprocedural myocardial injury. They are including strategy to prevent side branch occlusion, strategy to prevent distal embolization and microvascular coagulation, and strategy to protect myocardium.[3] Remote ischemic preconditioning (rIPC) is a method applying sub-lethal ischemic to target organs remote from the heart, such as small bladder, kidney, and the most non-invasive organ are the lower and upper extremities. rIPC decreases ischemic complication in both percutaneous coronary intervention and cardiac surgery procedure.[8,9] This procedure is safe, physiologic, non-invasive, simple, and inexpensive non-pharmacological method and potentially reduce periprocedural myocardial injury event. Patients with coronary artery disease (CAD) underwent PCI have risks for periprocedural myocardial injury and infarction, and this study found that remote ischemic preconditioning reduce periprocedural myocardial injury in patient PCI. However, the effect of rIPC remains elusive, and this study found that this rIPC reduce periprocedural myocardial injury but not infarction.

METHODS

Subject and design of study

This study was quasi-experimental, pre-posttest with control group design, in one center (Dr. Kariadi General Hospital, Semarang, Indonesia). Subjects of study were allocated into either intervention or control group by a simple randomization. Informed consent for participation in this study was obtained and the investigation was approved by the institutional ethics committee of human research in the

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Faculty of Medicine Diponegoro University and conformed with the principles outlined in the Declaration of Helsinki.[10]

The eligible subjects for inclusion in the study was patients with stable CAD underwent elective PCI. Patients with an increase of CK-MB level prior the PCI, acute coronary syndrome, chronic total occlusion (CTO) lesion, unstable hemodynamic (systolic blood pressure <90 mmHg and/or pulmonary edema), severe renal disease (creatinine serum level above 2.5 mg/dl), peripheral vascular disease, myo-skeletal injury or disease, malignancy, ore more than 70 years old were excluded from this study.

The baseline serum CK-MB was taken prior the PCI.[11] In the intervention group, a one hour rIPC prior PCI was performed by using a blood pressure cuff in the arm without intravenous line. The blood cuff was inflated 20 mmHg above patient's systolic blood pressure for 5 minutes, and then deflated for 5 minutes. This intervention was done for 4 cycles of ischemia-reperfusion.[12] The subject was dropped out if the PCI was postponed for more than 3 hours post rIPC protocol.[13] Angiographic characteristic and procedure, including lesion type, blood vessel target, pre-dilatation pressure and duration, length of stent, type of stent, thrombolysis in myocardial infarction (TIMI) flow post stent insertion, and complication post PCI were noted during PCI. Stent was inserted properly based on the clinical practice. All patients received bolus intravenous injection of unfractionated heparin with dose 70-100 *IU*/kg body weight. The second bolus heparin was given to maintain activated clotting time >250 seconds. Angiographic success was defined as residual stenosis <20% at the end of angiographic based on visual estimation. Procedural success was based on angiographic data and no major complication during hospitalization (acute myocardial infarction, need for emergency coronary artery bypass surgery or death). Complication after PCI was recorded. Those complication included side branch occlusion, dissection, distal embolization, arrhythmia, emergency coronary artery bypass surgery, acute myocardial infarction or death during hospitalization. Assessment of CK-MB level was done at 18 to 24 hours post PCI.[14,15]

Statistical analysis

SPSS software version 20.0 (Polar Engineering and Consulting, USA) was used for the statistical analysis. Mean differences between CK-MB level prior and post PCI were analyzed using the independent *t*-test or Mann-Whitney test as appropriate for continuous variables. The χ^2 test or Fisher's exact test was used as appropriate to compare categorical variables. The data were expressed in mean±SD. Differences with a *p* value of <0.05 were considered statistically significant.

RESULT

Baseline Characteristics

A total of 68 patients with CAD underwent elective PCI were enrolled. Nineteen patients were excluded and 7 patients were dropped out, and thus 42 patients were included for further analysis. They were randomized into intervention group (20 patients) and control group (22 patients). RIPC protocol was done successfully in all patients in the intervention group with no clinical evidence of arterial embolism, vein thromboembolism, or another complication. Clinical characteristics of subjects were shown in Table 1. The average of age was 58.47±5.96 years old. The most patients (78.5%) were male.

1.1 Angiographic and Procedural Characteristics

Most of patients had a single vessel stenting, including 13 (59.1%) patients in control group and 11 (55%) patients in intervention group (Table 2). The B type lesion based on the American Heart Association/ American College of Cardiology (AHA/ACC) criteria was found frequently in both groups. The number of *drug eluting stents* (DES) used was higher than non-DES, and they were placed mostly at left anterior descending artery (LAD). Almost of the stent installment procedure were preceded by pre-dilatation steps. There were no significant differences in angiographic characteristic and procedure between the intervention and control groups.

Table 1. Baseline Characteristics

Variables	Control (n=22)	rIPC (n=20)	*p*
Age	57.73±5.57	59.30±6.4	0.400
Male, n (%)	19 (86.3)	14 (70.0)	0.197
Body Mass Index ± SD	22.93±2.66	24.08 ± 2.91	0.186
LVEF (%), mean ± SD	56.60±9.19	56.25 ± 9.25	0.893
Traditional Risk factors			
Hypertension, n (%)	20 (90.9)	17 (85)	0.656
Diabetes Mellitus, n (%)	10 (45.5)	14 (70)	0.108
Active smoker, n (%)	5 (22.7)	3 (15)	0.767
Family history of premature CAD, n (%)	1 (4.5)	3 (15)	0.333
Hypercholesterolemia, n (%)	2 (9.09)	4 (20)	0.400
Pharmacological Therapy			
ACE-*inhibitors*, n (%)	12 (54.5)	10 (50)	0.768
Beta-*blockers*, n (%)	7 (31.8)	8 (40)	0.580
Nitrates, n (%)	17 (77.2)	13 (65)	0.379
Statin, n (%)	22 (100)	18 (90)	0.221
ARB, n (%)	5 (22.7)	2 (10)	0.269
Trimetazidine, n (%)	1 (4.54)	1 (5)	0.598

Statistical analyses were done using Mann-Whitney, except for age, body mass index and LVEF were using independent *t*-test.

Table 2. Angiographic and Procedural Characteristics

Variables	Control (n=22)	rIPC (n=20)	*p*
Target vessel revascularization, n (%)			
1 vessel	13 (59.1)	11 (55)	0.787[c]
2 vessels	7 (31.8)	8 (40)	
3 vessels	2 (9.1)	1 (5)	
Type of lesion (AHA/ACC)[16], n (%)			
Type A	3 (13.6)	1 (5)	0.591 [c]
Type B	14 (63.6)	15 (75)	
Type C	5 (22.8)	4 (20)	
Revascularized vessel, n (%)			
LAD	15 (68.18)	17 (85)	0.201 [c]
LCx	5 (22.7)	6 (30)	0.592 [c]
RCA	11 (50)	5 (25)	0.096 [c]
Others	4 (18.18)	3 (15)	0.782 [c]
Multi-vessels stenting, n (%)	10 (45.5)	9 (45)	0.976 [c]
Stenotic percentage, %, mean±SD	84.7±7.47	81.5±7.45	0.180[b]
Total stent length, mm, mean±SD	53.7±29,75	51.1±27.46	0.641 [b]
Overlapped stenting, n (%)	11 (50)	9 (45)	0.746[c]
Drug Eluting Stents, n (%)	10 (45.5)	14 (70)	0.108[c]
Fluoroscopic time, minute, mean±SD	24.83±16.69	24.03±12.74	0.862[a]
Direct stenting, n (%)	3 (13.6)	2 (10)	0.716[c]

[a]Independent t-test, [b]Mann-Whitney, [c]Chi-square

Table 3. Levels of CK-MB pre and post-PCI

Incidence	Control	rIPC	*p*
Periprocedural Myocardial Injury, n (%)	8(19.04)	1 (2.38)	0.022[a]
Periprocedural Myocardial Infarction, n (%)	2 (4.76)	0	0.489[a]

[a]Fisher's exact test

rIPC, remote Ischemic Preconditioning; LAD, Left Anterior Descending; LCx, Left Circumflex; RCA, Right Coronary Artery; AHA/ACC American Heart Association/ American College of Cardiology

1.2 Incidence of Periprocedural Myocardial Infarction and Injury

Table 3 shows that the level of CK-MB prior PCI was no significant difference between two groups, but its level post PCI was lower significantly in the intervention group than that of the control, 40.59±21.16 vs. 25.15±5.46 μg/mL, respectively (p=0.003). Thus, the delta level of CK-MB pre and post PCI was significant lower in the intervention group than that of the control, **6.15±3.88 vs. 22.0±20.0 μg/mL, respectively** (***p*=0.001).**

Table 4. Incidence of Periprocedural Myocardial Infarction and Injury

CK-MB	n	Mean ± SD, iu/L		*p*
		Control	rIPC	
Pre-PCI, mean±SD	42	18.59±3.17	19.00±2.90	0.665[a]
24 hour post-PCI, mean±SD	42	40.59±21.16	25.15±5.46	0.003[a]
Δ CKMB Pre-Post, mean±SD	42	22±20	6.15±3.88	0.001[b]

[a]Independent *t*-test, [b]Mann-Whitney

Furthermore, we observed periprocedural myocardial infarction and injury events in both groups. The periprocedural myocardial injury events were lower significantly in the intervention group than that of the control, 1 (2.38%) vs. 8 (19.04%), respectively (p=0.022), while the periprocedural myocardial infarction was not significant difference between the intervention and control groups, 0% vs. 2 (4.76%), respectively (p=0.489) (Table 4).

DISCUSSION

Remote ischemic preconditioning may potentially reduce periprocedural myocardial infarction and injury. The data of this study showed that four cycles of 5-minutes ischemia, followed by 5-minutes reperfusion in upper limb reduce the event of periprocedural myocardial injury in patient with CAD underwent elective PCI. Effects of remote ischemic preconditioning on myocardial injury have been reported by several studies, but its effectiveness remains elusive. Several factors affect the results, including the protocol used for rIPC, marker used to measure the outcome, subset of patients, and the use of cardioprotective agents such as statin.

Cardioprotective effect of rIPC was also showed by four other reports. [9,17-19] All of these studies used the same protocol for rIPC by performing three cycles of 5-minutes inflations of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-minutes intervals of reperfusion. They showed a similar outcome that rIPC prior to PCI attenuates the release of cardiac troponin at 16 to 24 post elective PCI. Our data in this study showed that rIPC prior to PCI reduce CKMB level at 18 to 24 hours post PCI, a finding that concur with result from a prior study by Liu et al.[17], while Ahmed et al.[19] reported that rIPC did not affect the CKMB level.

On the other hand, three studies reported that rIPC fails to show a significant effect on the level cardiac troponin release post elective PCI.[20-22] Yılmaztepe et al.[20] used one cycle of 5-minutes inflating the blood pressure cuff up to 200 mm Hg

on the non-dominant arm which may not reach an optimal ischemic preconditioning for myocardium. While Xu et al.[21] performed a 3 cycles of 5-minute pneumatic medical cuff inflations to 200 mm Hg in elderly patients with CAD having DM. These subset of patients may not get benefit from rIPC prior elective PCI since they could have mitochondrial dysfunction leading to failure in response to myocardial preconditioning.[23] Iliodromitis et al.[22] also used a three cycles of 5-minutes ischemia-reperfusion with blood pressure cuff inflated to 200 mmHg, but at both upper limbs, which was likely to induce inflammation reaction, shown by increase of level of C-reactive protein (CRP).

In regard with rIPC protocol, most of studies used a blood pressure cuff inflation to 200 mmHg for 5 minutes [9,17-19,22] ;however, in our clinical experience, this pressure is quite high and causes discomfort to the patients. Thus, the inflating blood pressure cuff 20 mmHg higher than systolic blood pressure in one arm was used in this study based on the rIPC protocol from McDonald et al.[24] which adjusted pressure according to the systolic blood pressure.[12] Both myocardial injury markers troponin and CK-MB have been used in the measurement of effectiveness of RIPC. We used CK-MB in this study because of it is more relevant and could be used to determine a prognosis implication when compared to troponin.[25]

The evidence of periprocedural myocardial infarction in this study was not significantly different between the intervention and control groups. The same finding was also reported by Ahmed et al.[19]. While Luo et al.[18] found that rIPC reduce the evidence of myocardial infarction related PCI. The statistical significance could be resulted from the different number of participants involved in those studies.

The mechanism how rIPC attenuate myocardial injury related PCI has been proposed in hypothesis. A current study found that rIPC induces an intracoronary increase of nitric oxide levels associated with a decrease in myocardial damage measured as no increase in cardiac troponin I with electrocardiographic increases in the sum of R waves, suggesting an improved myocardium after elective PCI.[26]

CONCLUSION

Remote ischemic preconditioning may reduce periprocedural myocardial injury in patient with coronary artery disease underwent elective percutaneous coronary intervention. Several prior reports,[9,17-19,22] corroborate the finding that rIPC as a safe and effective strategy to protect myocardium during elective PCI. It could be applied routinely in clinical practice since it is non-invasive, easy, cheap, and safe procedure, with no complication event.

STUDY LIMITATION

Limitation of this study is that the patients who used intracoronary glyceryl trinitrate during PCI were not excluded. This agent is known to have a preconditioning-mimetic effect in both experimental group and control group.[27] The CK-MB level was measured in a single blood sample obtained 18 to 24 hours post PCI rather than defining the CK-MB release profile every 4 to 6 hours. The resultant value may not be the maximum plasma concentration, although it is generally accepted that the maximum concentration occurs between 16 and 30 hours after myocyte necrosis.

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