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Effect of remote ischemia or nicorandil on myocardial injury following percutaneous coronary intervention in patients with stable coronary artery disease: A randomized controlled trial☆

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ABSTRACT

Background: The effect of remote ischemic preconditioning (RIPC) and nicorandil on periprocedural myocardial injury (pMI) in patients with planned percutaneous coronary intervention (PCI) remains controversial. The aim of this randomized trial was to evaluate the effect of RIPC or nicorandil on pMI following PCI in patients with stable coronary artery disease (CAD) compared with a control group.

Methods: Patients with stable CAD who planned to undergo PCI were assigned to a 1:1:1 ratio to control, RIPC, or intravenous nicorandil (6 mg/h). Automated RIPC was performed by a device, which performs intermittent arm ischemia through three cycles of 5 min of inflation and 5 min of deflation of a pressure cuff. The primary outcome was the incidence of pMI, determined by an elevation in high-sensitive troponin T or creatine kinase myocardial band at 12 or 24 h after PCI. The secondary outcomes were ischemic events during PCI and adverse clinical events at 8 months after PCI.

Results: A total of 391 patients were enrolled. The incidence of pMI following PCI was not significantly different between the control group (48.9%) and RIPC group (39.5%; $p = 0.14$), or between the control group and nicorandil group (40.3%; $p = 0.17$). There were no significant differences in ischemic events during PCI or adverse clinical events within 8 months after PCI among the three groups.

Conclusions: This study demonstrated moderate reductions in biomarker release and pMI by RIPC or intravenous nicorandil prior to the PCI consistently, but may have failed to achieve statistical significance because the study was underpowered.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Periprocedural myocardial injury (pMI) is a major complication of percutaneous coronary intervention (PCI) in patients with stable coronary artery disease (CAD). This condition is recognized as a predictor of long-term adverse clinical outcomes [1,2]. The potential contributing mechanisms for pMI following PCI in patients with stable angina include downstream embolization of atheromatous material and coronary side-branch occlusion [3–5]. Several drugs have been tested to increase cardiac tolerance to ischemic injury [3,6,7]. Nicorandil activates potassium channels in mitochondria, and this plays a beneficial role in mimicking ischemic preconditioning. Intravenous nicorandil was reported to reduce pMI or slow flow phenomenon following PCI in patients with planned and emergent PCI [8,9]. Remote ischemic preconditioning (RIPC) is defined as when transient nonlethal ischemia and reperfusion applied to one organ or tissue protects another organ or tissue from a subsequent episode of lethal ischemia and reperfusion [10]. RIPC by upper or lower limb ischemia can reduce ischemic reperfusion injury in patients undergoing elective PCI [11–16]. However, several conflicting results of RIPC in patients with planned PCI have been reported recently [17–19,20]. Only a few studies with a small sample size and from a single center have been conducted.

The aim of this study was to investigate the efficacy of RIPC or intravenous nicorandil on pMI in patients with stable CAD undergoing elective PCI by a randomized, multicenter trial. To improve the reproducibility of RIPC, we have developed a device, which can automatically repeat ischemia and reperfusion in the upper limbs.

2. Methods

2.1. Patient population

This study was a prospective, open label, multicenter, randomized, controlled trial, which was conducted at 18 hospitals between June 2011 and January 2013. The study was approved by the ethics committees of all hospitals. All participants provided written informed consent before enrolling. This study was conducted according to the principles expressed in the Declaration of Helsinki. The study is registered at the UMIN Clinical Trials Registry (UMIN000005607).

Eligible patients were adults (>20 years old) who were diagnosed with stable CAD including silent myocardial ischemia and stable angina and planned to have elective PCI. All patients underwent coronary angiography before enrollment of this study. Indication of PCI was evaluated according to the guideline for elective percutaneous coronary intervention in patients with stable coronary artery disease from the Japanese Society of Cardiology [21]. Patients were excluded for the following reasons: they had acute coronary syndrome, there was contraindication of intravenous nicorandil administration, they planned elective PCI for chronic total occlusion lesion or PCI with a rotablator, use of sulfonylurea, an aorta-venous shunt was present in the arms, and prognosis was regarded as <12 months. We obtained written informed consent from all enrolled patients

2.2. Study protocol

Patients were randomly assigned in a 1:1:1 ratio to control, intravenous nicorandil (6 mg/h), or RIPC. Randomization was conducted by the Clinical Trials Unit based at Okayama University via a secure website and was stratified by the center using random permuted blocks. In the patients who were assigned to the RIPC group, 5-minute inflation of a blood pressure cuff to 200 mmHg around the upper arm, followed by 5-minute deflation of a cuff to 0 mmHg was performed three times at least 1 h before PCI. This procedure was automatically performed by a newly developed automated continuous blood pressure device (FB-270; Fukuda Denshi, Tokyo, Japan) [22]. In the patients who were assigned to the nicorandil group, 4 mg of nicorandil was intravenously administered for 5 min at least 1 h before PCI, followed by continuous infusion of nicorandil (6 mg/h) for at least 8 h. Stopping the infusion was dependent on the practice of each hospital. Patients in the control group did not receive any additional pre-treatment before PCI.

PCI was performed in a conventional manner as previously reported. Complexity of coronary lesions was assessed according to AHA-ACC classification, including types A and B1 or B2 and C. All of the procedures depended on the practice of each hospital. The perfusion status of the target-related coronary artery was determined in accordance with the Thrombolysis In Myocardial Infarction (TIMI) study classification [23]. The final TIMI flow grade was assessed from the final angiography image. Coronary stenosis was assessed by angiography or fractional flow reserve.

Blood samples for high-sensitive cardiac troponin T (cTnT) and creatine kinase myocardial band (CK-MB) were collected at 12 and 24 h after PCI. To avoid inter-hospital variation of high-sensitive cTnT and CK-MB levels, these markers were evaluated at a single institution (SRL Inc. Hachioji Laboratory, Tokyo, Japan). Study investigators who collected and analyzed the data were blinded to the treatment assignments.

2.3. End points

The primary end point was the incidence of pMI following PCI. The definition of pMI was as follows: an elevation in high sensitive cTnT levels >0.07 ng/ml (5 × 99th percentile upper reference limit); or CK-MB levels >10 ng/ml and CK-MB/creatinine kinase levels >5%, at 12 h or 24 h after PCI. In case of patients being discharged before regular assessment, these cardiac biomarkers were assessed at discharge.

At the time of planning the protocol, myocardial injury was defined as an elevation in levels of non-high sensitive cTnT >0.03 ng/ml; or CK-MB levels >10 ng/ml and CK-MB/creatinine kinase levels >5%, at 12 or 24 h after PCI. However, at the time of starting this study, the cTnT which was measured in the core laboratory was changed from non-high sensitive cTnT to high sensitive cTnT. Therefore, the cutoff value of cTnT was revised based on the diagnostic criteria for myocardial infarction with PCI from the third universal definition of myocardial infarction, which had changed in 2012 [24].

The secondary end points were ischemic events during PCI, including the procedural success rate, chest pain during PCI, ST segment change on an electrocardiogram (≥1 mV) during PCI, ventricular arrhythmia needed for cardioversion during PCI, and final TIMI grade. We also studied adverse clinical events at 8 months after PCI as a secondary end point. Adverse clinical events included cardiovascular or non-cardiovascular death, admission for acute coronary syndrome, any revascularization, and admission for heart failure.

2.4. Statistical analysis

Efficacy analyses were performed in the full analysis set, which was defined as all randomized patients who received any protocol treatment and PCI, and their eligibility was confirmed. Although the supplemental per protocol set for efficacy analyses was also defined, the results are not shown in this article. Safety analyses were conducted for all randomized patients. In efficacy analyses, patients with abnormal cTnT, CK-MB, and/or CK-MB/CK values (high-sensitive cTnT: >0.014 ng/ml, CK-MB: >5 ng/ml, and CK-MB/creatinine kinase: >5%) were additionally analyzed.

We assumed that the proportion of pMI following PCI was 30% in the control group and 12% in the RIPC and nicorandil groups, based on previous reports [8,16,25,26]. Multiplicity adjustment was not applied because the RIPC and nicorandil groups were separately compared and interpreted with the control group. To assure that the two-sided significance level was 5% and the power was 90%, 106 patients in each group were required. Assuming that approximately 20% of patients would drop out and/or abnormal values would be detected at pre-PCI, we set the sample size as 133 patients per group.

In primary analysis, Fisher's exact test was applied to compare proportions of pMI following PCI between the RIPC and control groups or the nicorandil and control groups. The risk differences of proportions between groups and their 95% confidence intervals (CIs) were calculated. Additionally, a logistic regression model was used to calculate odds ratios (ORs) between study groups with adjustment for age (<65 or ≥65 years old), sex, and with or without chronic kidney disease (estimated glomerular filtration rate [eGFR] at baseline <60 or ≥60 ml/min/1.73 m^2). The Mann–Whitney *U* test was applied to compare the levels of high sensitive cTnT following PCI between the RIPC and control groups or nicorandil and control groups.

The same analyses of the primary end point were applied to ischemic events during PCI. For adverse clinical events at 8 months after PCI, the Kaplan–Meier estimate was used by treatment group and compared using the log-rank test. Cox's proportional hazard model was used to estimate hazard ratios (HRs) between treatment groups. We also evaluated the effect of RIPC and intravenous nicorandil for the primary end point in subgroups defined by the following baseline characteristics: age (<65 years old or ≥65 years old), sex, with or without chronic kidney disease (eGFR at baseline <60 ml/min/1.73 m^2 or eGFR at baseline ≥60 ml/min/1.73 m^2), with or without diabetes, smoking history (current smoker, ex-smoker, or never smoker) and AHA-ACC classification of PCI lesion (types A and B1 or B2 and C).

We also used a repeated-measures linear mixed-effects model to assess troponin and CK-MB as continuous variables. To account for non-normality, these endpoints were natural log-transformed and used as dependent variables. Independent variables in this model were log-transformed baseline troponin or CK-MB, age category, sex, chronic kidney disease status, treatment arm, scheduled visit as a class variable (12 h, 24 h) and the interaction between the arm and the visit, with the use of an unstructured covariance matrix. We used the residual maximum likelihood (REML) method for estimation. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. Least square mean estimates and their 95% confidence intervals were exponentially back-transformed.

Continuous variables are presented as means ± standard deviation or as medians with interquartile range. Categorical variables are presented as numbers and ratios (%). Continuous variables were compared with the use of analysis of variance or the Kruskal–Wallis test for non-normally distributed data. All analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A p value of <0.05 was considered statistically significant.

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