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Efficacy of electroacupuncture pretreatment for myocardial injury in patients undergoing percutaneous coronary intervention: A randomized clinical trial with a 2-year follow-up

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ABSTRACT

Electroacupuncture pretreatment (EAP) safely protects the heart from ischemic injury, however, the efficacy of EAP for periprocedural myocardial injury after percutaneous coronary intervention (PCI) remains unclear. Our aim was to investigate whether EAP prior to PCI reduces post-PCI myocardial injury in patients with coronary artery disease (CAD). 388 patients (≥18 years old) with CAD, undergoing elective PCI were enrolled and randomized, out of those 204 went through the whole trial. EAP was conducted by 30-minute electrical stimulation through 4 electrodes attached to the Antiguan (PC6) and Ximen (PC4) acupoints in the forearm bilaterally 1–2 h prior to PCI. The control group had sham electrodes but no electrical stimulation. The primary end point was the incidence of myocardial infarction type 4a (MI4a) based on serum cTnI values at 24 h after PCI. The secondary end points included post-procedural cardiac function and the major adverse cardiac/cerebrovascular event (MACCE) rate. EAP prior to PCI significantly reduced the incidence of MI4a (serum cTnI ≥ 0.20 ng/mL) 24 h post-PCI compared to the control group ($P = 0.004$). The echocardiography at 6 months after PCI revealed significant improvement in cardiac function in the EAP group compared with the control group. The MACCE rate was significantly decreased in the EAP group at 24 month follow-up compared to the control group ($P = 0.0157$). Moreover, multivariate logistic regression analysis showed that EAP was associated with decreased likelihood of MACCE (odds ratio 0.327, 95% CI 0.140–0.767, $P = 0.010$). EAP prior to PCI significantly reduced cTnI release and protected patients with CAD from subsequent myocardial injury after PCI procedure.

1. Introduction

The current therapy for coronary artery disease (CAD) relies increasingly upon percutaneous coronary intervention (PCI). Unfortunately, some cardiac complications during PCI, such as artery dissection, acute thrombosis formation, slow reflow or branch vessel occlusion, may independently trigger subsequent myocardial injury and heart dysfunction [1]. Approximately one-third of all elective PCI procedures are complicated by myocardial injury, with subsequent cardiovascular events (including arrhythmias, cardiac dysfunction) and mortality [2]. Increased serum cardiac enzymes, including cardiac troponin I (cTnI), occur in more than 25% of post-PCI patients [3,4]. A wealth of evidence supports the correlation of extensive cardiac enzyme release after PCI with cardiac injury [5,6] and delayed mortality [7,8]. Statins [9], beta-blockers [10], cyclosporine [11] and trimetazidine [12] have been reported to limit the rate and extent of PCI-associated myocardial infarction (MI type 4a) [13]. Moreover, non-pharmacological interventions, such as remote ischemic preconditioning, also provide effective protection against PCI-related myocardial injury [14,15]. However, peri-procedural myocardial injury after PCI remains unresolved.

Acupuncture is practiced and accepted worldwide as a promising alternative therapeutic approach in treating diseases such as migraine [16], chronic low back pain [17], and knee osteoarthritis [18]. It also improves exercise tolerance in heart failure patients [19]. A recent clinical trial demonstrated that an acupuncture-assisted anesthesia reduced postoperative morbidity and medical costs in an open-heart surgery cardiopulmonary bypass procedure [20]. Our previous studies

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also proved that electroacupuncture pretreatment [EAP, 30-minute electric stimulation through 4 electrodes attached to the bilateral forearm Neiguan (PC6) and Ximen (PC4) acupoints] before surgery significantly attenuated serum cTnI levels during and shortly after surgery in adults undergoing heart valve replacement [21] and in children undergoing cardiac surgery for correcting congenital heart malformation [22]. However, whether EAP attenuates periprocedural myocardial injury after PCI, especially in those patients exhibiting complex coronary lesions, has not been previously investigated. Therefore, the current multi-center clinical trial was designed to evaluate whether EAP reduces PCI-related myocardial injury.

2. Methods

2.1. Study design

This clinical study was a prospective, randomized, multi-center trial, conducted in 5 central hospitals in China (ClinicalTrials.gov # NCT01020942). The study was approved by the Institutional Ethics Review Committees at all participating hospitals, and the study protocol conformed to the principles outlined in the Declaration of Helsinki. An independent data and safety monitoring board met at least twice annually to oversee the trial. No formal termination rules were specified. The academic members of this trial had full access to all study data, to vouch for its accuracy, complete data analyses, verify protocol fidelity in the study's conduct, write up the manuscript, and were ultimately responsible for its integrity. The research protocol summary is currently available at ClinicalTrails.gov (NCT01020942).

2.2. Patients

388 patients, who were at least 18 years old with a diagnosis of stable or unstable angina, or silent ischemia, undergoing non-urgent coronary angiography with the intention to undergo elective percutaneous coronary intervention (PCI), and able to give informed consent, were enrolled and randomized. Out of those 204 patients went through the whole trial and were analyzed. Patients underwent angiography, and were diagnosed with one, two, or three-vessel diseases with diameter stenosis ≥70%. Inclusion and exclusion criteria are provided in the Supplementary Appendix. All patients provided written consent.

2.3. Treatment and blinding

All the study patients received medication prior to PCI in accordance with current ACCF/AHA/SCAI guidelines for the clinical management of patients with coronary artery disease [23]. Participants were randomly assigned to groups, in a 1:1 ratio, to receive EAP or control (sham pretreatment). The randomization sequence was computer-generated, and randomization was performed in blocks of randomly varying sizes and was stratified according to participating hospital. Interventionists conducting PCI, measurements of cTnI and inflammatory markers, positron emission tomography/computed tomography (PET/CT) imaging, echocardiography, and telephone follow-up were blinded. The acupuncturists performing EAP who were unmasked to treatment assignments, did not participate in data acquisition and analysis. EAP protocol utilized was 30-minute electrical stimulation through 4 electrodes attached to the Neiguan (PC6) and Ximen (PC4) acupoints in the forearm bilaterally 1–2 h prior to PCI. The control group patients had the same electrodes applied and received sham treatment based on previously described design for patient blinding [24,18]. Details regarding the EAP and PCI procedures are provided in the Supplementary Appendix.

2.4. End points and follow-up

Baseline serum cTnI levels were measured in all patients prior to PCI. The primary end point was the incidence of MI4a based on serum cTnI values at 24 h after PCI. MI4a is arbitrarily defined by the elevation of cardiac troponin values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) according to the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction [25]. The secondary end points included post-procedural cardiac function and the major adverse cardiac/cerebrovascular event (MACCE) rate. To evaluate cardiac function in all patients, echocardiography was performed at pre-, 3 and 6 months post-PCI intervals. The MACCE rate was followed up either by clinic visits or by telephone interviews as deemed necessary for 24 months in all 204 patients.

To elucidate potential beneficial effects of EAP, serum levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and high mobility group box 1 (HMGB1) were measured at pre-PCI and 24 h post-PCI. Additionally, patients with left anterior descendant coronary stenosis underwent PET/CT imaging at pre- and at 3 days post-PCI intervals to assess myocardial metabolic activity. Details regarding end point measurements are provided in the Supplementary Appendix. All clinical end points were assessed in a blinded fashion. All serological samples were analyzed in the clinical laboratory of Xijing Hospital.

2.5. Sample size and statistical analysis

The trial was conducted to determine whether EAP was beneficial for reduction in the incidence of MI4a with respect to the primary end point. According to our preliminary pilot data, about 50% of patients have myocardial injury complications after elective PCI procedures. The incidence of the primary end point was estimated to be 40% reduction in patients randomized to the EAP group. Therefore, the minimum number of patients necessary for this trial to enable detection of such reduction at a two-sided type I error rate of 0.05 ($\alpha = 0.05$) and power of 0.80 ($\beta = 0.20$) was 182 total (91 per group).

All patients were included in the analysis according to groups of original assignment (intention-to-treat analysis). Continuous variables were presented as means and standard deviations (SD) or standard error of the mean (SEM), and categorical data as numbers and percentages. Because cTnI data were skewed, these values were expressed as median with interquartile range (IQR). Baseline clinical and angiographic characteristics and procedural data were compared between the two groups by the Student's *t*-test or *t′*-test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables whenever appropriate. The differences in time course of echocardiographic parameters between study groups and among time points within each group were analyzed by repeated measures analysis of variance. Multivariate logistic regression was constructed to test the association of EAP and MACCE. Covariates included EAP, men sex, age, diabetes mellitus, hypertension and previous MI. Patients with missing values in one of the co-variables were excluded from analysis. Data were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The incidences of MACCE rate was estimated by the Kaplan–Meier method. For each individual, missing values were replaced by the last observed variable value (last observation carried forward). SPSS software package version 19.0 (SPSS, Chicago, IL) was used for data analysis. A *P* value of less than 0.05 was considered significant.

3. Results

3.1. Baseline clinical characteristics and study termination

At the recommendation of the independent data and safety monitoring board, patient recruitment was terminated on September 18, 2011. 420 patients with CAD were enrolled. 32 patients registered were not