ORIGINAL ARTICLE

Effect of Danlou Tablet (丹蒌片) on Peri-procedural Myocardial Injury among Patients undergoing Percutaneous Coronary Intervention for Non-ST Elevation Acute Coronary Syndrome: A Study Protocol of A Multicenter, Randomized, Controlled Trial

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ABSTRACT Background: It has been shown that administration of statins reduced the risk of peri-procedural myocardial damage. However, it remains unclear whether Chinese medicine Danlou Tablet (丹蒌片), similar to statins, may protect patients undergoing percutaneous coronary intervention (PCI) from peri-procedural myocardial damage. Objective: To demonstrate the hypothesis whether treatment with Danlou Tablet would improve clinical outcome in patients undergoing selective PCI with non-ST elevation acute coronary syndrome (NSTE-ACS) in China. Methods: Approximately 220 patients with unstable angina or non-ST-segment elevation myocardial infarction undergoing PCI will be enrolled and randomized to Danlou Tablet treatment (4.5 g/day for 2 days before intervention, with a further 4.5 g/day for 90 days thereafter) or placebo. All patients will not receive Danlou Tablet before procedure. The primary end point is to evaluate the incidence of cardiac death, myocardial infarction or unplanned re-hospitalization and revascularization after 30 days in patients undergoing selective PCI treated with Danlou Tablet compared with placebo. Secondary endpoints include the incidence of peri-procedural myocardial injury, 3-month clinical outcomes, the quality of life and Chinese medicine syndromes assessment. Conclusion: This study protocol will provide important evidence of Danlou Tablet treatment on the peri-procedural myocardial injury in patients with NSTE-ACS undergoing selective PCI, which may support a strategy of routine Danlou Tablet therapy to improve the clinical outcomes.

KEYWORDS non-ST-segment elevation acute coronary syndrome, percutaneous coronary intervention, Danlou Tablet, peri-procedural myocardial infarction, Chinese medicine

Over the past few years, a high incidence of adverse cardiovascular events following percutaneous coronary intervention (PCI), including peri-procedural myocardial injury, received a great deal of attention in spite of major improvements in this therapy. As estimated, 75,000 to 450,000 patients with coronary artery disease have sustained a peri-procedural myocardial injury, in which the incidence is similar to the annual rate of spontaneous myocardial infarction. Peri-procedural myocardial injury, also known as myocardial necrosis was assessed by cardiac biomarker elevation. As many retrospective observational studies found that the extent of cardiac biomarkers increase is related to subsequently adverse cardiovascular events and mortality rate. Despite many strategies have been proposed to address this issue, procedural ischemic myocardial injury remains the primary complication after coronary angioplasty.

Recently, many clinical trials demonstrated the efficacy of 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) in significant reduction of peri-procedural myocardial infarction in patients with acute coronary syndromes following coronary intervention. For instance, the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) trial revealed that treatment with atorvastatin in statin-naive patients undergoing selective PCI for chronic stable angina was associated with a considerable decrease in the occurrence of peri-procedural myocardial...
injury. This myocardial protection was confirmed by the ARMYDA-ACS (Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes) trial, in which a pre-treatment with high-dose atorvastatin 12-h prior to procedure of coronary revascularization in statin-naive patients with acute coronary syndromes undergoing early invasive strategy improved outcomes during a period of 30-day follow-up. Furthermore, the ROMA (Rosuvastatin Pretreatment in Patients Undergoing Elective PCI to Reduce the Incidence of Myocardial Periprocedural Necrosis) trial established that a single, high loading dose of rosuvastatin (40 mg) within 24 h before elective PCI in patients with stable coronary artery disease could decrease the rate of post-procedural elevation of cardiac biomarkers compared with the standard treatment. Nevertheless, high-dose or even super-high-dose statin pretreatment and maintenance might increase the risk of liver damage or rhabdomyolysis. Therefore, numerous studies, including that presented in this paper, aim at elucidating whether such myocardial injury could be averted after administration of some natural herbs or agent that reduce the incidence of peri-procedural myocardial necrosis after non-emergency coronary angioplasty.

Chinese medicine (CM) has been practiced for thousands of years and a series of studies have suggested that it bring multiple benefits to people with coronary heart disease (CHD) due to the discovery of their effectiveness in alleviating symptoms of myocardial infarction, angina pectoris, arrhythmia, hypertension and other cardiovascular conditions. In particular, Danlou Tablet (丹蒌片), a Chinese patent medicine, has been successfully utilized by many cardiologists and internists for its induction of promoting blood circulation and eliminating phlegm. It consists of the following ingredients: Salvia, miltiorthiza Bunge, Ligusticum chuanxiong Hort, Trichosanthes kirilowii Maxim and Allium macrostemon Bunge, etc.

Moreover, recent experimental research has indicated that Danlou Tablet may reduce blood lipid level of rats with hyperlipidemia and improve vascular endothelial function in rats with arterial endothelial injury. In addition, it could reduce myocardial necrosis area and promote infarct healing, prevention and treatment of early left ventricular remodeling in rats exposed to myocardial ischemia-reperfusion injury. Importantly, a multicenter trial demonstrated that administration of Danlou Tablet improved clinical symptoms, inhibited the inflammation reaction of patients with CHD and decreased the frequency of major atherogenic complications (plaque rupture and thrombosis). Thus, we hypothesized that administration of Danlou Tablet may provide benefits for myocardial necrosis in patients with acute coronary syndrome (ACS) undergoing invasive surgery, which is similar to statins.

METHODS

Aim of the Study
The primary objective is to evaluate the major adverse cardiac clinical events (MACE) in terms of cardiac death, peri-procedural myocardial infarction (MI), spontaneous MI and target vessel revascularization (TVR). According to the literature, the peri-procedural MI was defined as a creatine kinase-MB (CK-MB) elevation >3 upper limit of normal (ULN) value alone or associated with chest pain in patients undergoing PCI. The secondary objective is to evaluate the efficacy of the sequential peri-PCI Danlou Tablet treatment strategy, which means pre-PCI loading doses of Danlou Tablet and post-PCI Danlou Tablet treatment for 30 days, in reducing 30-day primary cardiovascular endpoints in patients undergoing PCI with non-ST elevation acute coronary syndrome, and the rate of peri-procedural rise of myocardial biomarkers (troponin I and CK-MB and hyper sensitive C-reactive protein (hs-CRP) greater than the normal value within 8 and 24 h after PCI. In addition, the effect of Danlou Tablet treatment on the serum level of triglycerides and cholesterol, and the efficacy of peri-procedural CM therapy on clinical outcomes including quality of life and CM syndromes 3 months following surgery will also be investigated.

Study Design
This is a multicenter, randomized, prospective, double-blind, placebo-controlled, parallel-group study performed in 9 institutions (Guangdong Provincial Hospital of Chinese Medicine; Xiyuan Hospital of China Academy of Chinese Medical Sciences; Yueyang Hospital of Integrated Medicine of Shanghai University of Chinese Medicine; Dongfang Hospital of Beijing University of Chinese Medicine; First Affiliated Hospital of Zhejiang University of Chinese Medicine; China-Japan Friendship Hospital of Ministry of Health; Affiliated Hospital of Guangdong Medical College; First Affiliated Hospital of Henan College of Chinese Medicine; Tianjin...