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Original article

Self-emulsifying drug delivery system improves preventive effect of curcuminoids on chronic heart failure in rats

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ABSTRACT

Several studies have reported the preventive or therapeutic effect of curcuminoids on chronic heart failure (CHF), but their application was limited due to low solubility and bioavailability. Our previous study indicates that self-emulsifying drug delivery system (SEDDS) improves the solubility and bioavailability of curcuminoids. Thus, the aim of this work was to investigate whether SEDDS could improve preventive effect of curcuminoids on CHF in rats. CHF model was were established by coronary artery ligation. Ninety rats were randomly and averagely divided into sham, model, low- or high-dose suspension or SEDDS of curcuminoids (66.68 or 266.68 mg/kg) groups. Hemodynamic indices were recorded by multi-purpose polygraph. Serum oxidative indices, B-type natriuretic peptide (BNP) and heart weight index were determined by kits and electronic balance. Myocardial infarct area, ventricular dilatation degree and collagen volume fraction of myocardial interstitium were analyzed by Masson staining, picric acid and sirius red staining, light microscopy and image analysis system. Myocardial histopathology was observed by hematoxylin and eosin staining, Masson staining and light microscopy. Reduction of ventricular pump function, increase of BNP level and heart weight index, myocardial lipid peroxidation damage, myocardial infarction, myocardial fibrosis, and cardiac enlargement were detected or observed in model group relative to those in sham group. After treatment with suspension or SEDDS of curcuminoids, the above-mentioned pathological changes were obviously reversed relative to those in model group. Meanwhile, the ameliorative effect of SEDDS of curcuminoids was markedly better than that of suspension of curcuminoids. This work provides a valuable reference from pharmacodynamics for development of curcuminoids pharmaceutics.

1. Introduction

Heart failure (HF) is characterized by the obvious reduce of cardiac output leading to the perfusion deficiency of blood in systemic organ. Generally, pulmonary or systemic circulation venous congestion are simultaneously diagnosed in HF patients, so HF can also be known as congestive HF (Stewart and Givertz, 2012). HF is a major public health problem, with a prevalence of more than 23 million worldwide (Roger, 2013). With the evolution of epidemiology and development of social economy in China, the Chinese epidemiological character of HF is more close to that of developed country. For example, coronary heart disease-induced HF in China becomes more and more prominent (Jiang and Ge, 2009). Gratifyingly, with the deeper cognition to pathophysiological mechanism and development of biomedical engineering technology, the clinical therapy of HF has entered into the era of multi-therapy, such as drugs, cardiac resynchronization, stem cell and heart transplantation. The survival quality and prognosis of patients with HF are significantly improved after treatment with multi-therapy (Li and Wang, 2005). However, the patients with end-stage HF still face high mortality risk. Meanwhile, a large number of clinical reports indicate that traditional Chinese medicines (TCMs) show good

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clinical effect on HF, so it is vital to develop TCMs for treating HF and offsetting the deficiency of Western medicine in treating HF (Li et al., 2013; Liu et al., 2011).

TCMs from *Curcuma*, such as Curcumae Longae Rhizoma, Curcumae Rhizoma and Curcumae Radix, show therapeutic and preventive effect on cardiovascular diseases, such as chronic heart failure (CHF) and platelet aggregation (Gao, 2017; Wang and Wang, 2001). Curcuminoids, mainly including curcumin, demethoxycurcumin and bisdemethoxycurcumin, is the main therapeutic material basis of TCMs from *Curcuma* and show protective effect on heart function (Morimoto et al., 2008; Nabavi et al., 2011). However, the application of curcuminoids was limited due to low solubility and bioavailability (Kakkar et al., 2011). The early study in our team indicates that self-emulsifying drug delivery system (SEDDS) improves the solubility and bioavailability of curcuminoids (Ke et al., 2014). Based on the results of the early study, this work was designed to investigate whether SEDDS could improve preventive effect of curcuminoids on CHF in rats.

2. Material and methods

2.1. Chemicals and regents

Curcuminoids, mainly including 82.22% curcumin, 12.43% demethoxycurcumin and 2.44% bisdemethoxycurcumin, was purchased from Nanjing Zelang Biological Technology Co., Ltd (Nanjing, China). The suspension and SEDDS of curcuminoids were prepared with 0.5% sodium carboxyl methyl cellulose (CMC-Na) solution and the reported method (Ke et al., 2014). Ethyl carbamate and benzylpenicillin sodium were obtained from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China) and North China Pharmaceutical Co., Ltd (Shijiazhuang, China), respectively. B-type natriuretic peptide (BNP), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) and malonaldehyde (MDA) kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

2.2. Animals

Specific pathogen-free male SD rats (180 ± 20 g) were provided by the Experimental Animal Center, China Three Gorges University (Yichang, China) and were housed in a temperature-controlled vivarium (22 ± 2 °C) with relative humidity of 60 ± 5% and 12/12-h light-dark cycle. All rats have free access to water and food. All animal treatments were conducted in strict compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (The National Research Council of The National Academy of Sciencies, 2010). All experiments involved animals in this work were performed with the approval of the Ethics Committee of China Three Gorges University.

2.3. Replication of CHF model in rats

Before operation, the electrocardiography of each rat was monitored by Biopac MP150 multipurpose polygraph (Goleta, CA, USA). Rats with normal electrocardiography were used to establish CHF model by coronary artery ligation according to previous procedure (Li et al., 2011). Briefly, after rats were anesthetized by intraperitoneal injection of 20% ethyl carbamate (1.5 g/kg), coronary artery ligation was achieved with a gab occluder fixed onto the left anterior descending coronary artery. A 6-0 silk suture was passed underneath the left anterior descending (1–2 mm inferior to the left auricle) and tied. The electrocardiography of rat was instantly monitored. If the electrocardiography ST segment elevation was observed, the coronary artery ligation was successfully performed. Then, the chest was closed in layers, and the respirator weaned when the rat recovered spontaneous breathing. Subsequently, rats were subcutaneously injected with normal saline (30 mL/kg) to replenishing fluid loss and were locally treated with povidone-iodine and benzylpenicillin sodium to disinfection and anti-infection. Sham-operated rats underwent all the above-described surgical procedures, except that the 6-0 silk suture, passing around the left anterior descending, was not tied.

2.4. Animal grouping and treatment

Ninety rats were randomly and averagely divided into sham, model, low- or high-dose suspension of curcuminoids (66.68 or 266.68 mg/kg), and low- or high-dose SEDDS of curcuminoids (66.68 or 266.68 mg/kg) groups. At 0.5 h before coronary artery ligation operation, rats in sham and model groups were administrated orally with distilled water, and rats in other groups were administrated orally with corresponding drugs. After operation, rats were administrated based on the above-described treatment once a day for 8 weeks.

2.5. Hemodynamic assessment

At 24 h after last administration, rats were weighed by Ohaus AR3130 electronic balance (Pinebrook, NJ, USA) and anesthetized by intraperitoneal injection of 20% ethyl carbamate (1.5 g/kg). A venous cannula was inserted into the left ventricular cavity of rat through the right common carotid artery. Then, heart rate (HR), left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximal rate of the increase of left ventricular pressure ($+dp/dt_{max}$), maximal rate of the decrease of left ventricular pressure ($-dp/dt_{max}$) were recorded with the aid of Biopac MP150 multipurpose polygraph (Goleta, CA, USA). The mean of 5 segments recorded value of above-described hemodynamic indices was used for statistical analysis.

2.6. Determination of serum oxidative indices and BNP levels or activities

After determination of hemodynamic indices, the abdominal aortic blood of each rat was collected and centrifuged at 3500 rpm for 15 min at 4 °C to obtain serum, which was stored at −20 °C for further analysis. Serum oxidative indices (SOD, GSH-Px, CAT and MDA) and BNP levels or activities were determined using corresponding kits according to the manufactures' instruction for each. After reactions were completed, absorbance of each index in each sample was determined using Unico UV-2000 UV–VIS spectrophotometer (Shanghai, China) or Awareness Stat Fax-2100 microplate reader (Palm, FLA, USA). The absorbance for each index was used to calculate its level or activity according to corresponding standard curve.

2.7. Determination of heart weight index

After collecting abdominal aortic blood, rat was sacrificed by decapitation, and its heart was removed and washed with 4 °C normal saline, blotted with a piece of filter paper and weighed by Mettler-Toledo AL204 electronic balance (Shanghai, China). Heart weight index was calculated as heart weight (mg)/body weight (g).

2.8. Determination of myocardial infarct area and ventricular dilatation degree

Left ventricle of rat was cut into five equal parts along the long axis from cardiac apex to base, and the myocardial fragment of maximum ventricular perimeter was fixed in 10% formalin. The

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