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Evaluation of low-dose colchicine in patients with cardiopulmonary bypass: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Inflammation and myocardial damage caused by cardiovascular surgery with cardiopulmonary bypass (CPB) have been shown to be the major contributors to postoperative morbidity and mortality. Colchicine can reduce myocardial ischaemia-reperfusion injury in patients with chronic coronary artery disease. However, there is a lack of evidence whether colchicine could reduce myocardial injury after cardiovascular surgery. In this study, we aim to evaluate the effect of low-dose colchicine on myocardial protection during perioperative period in patients who undergo cardiovascular surgery with CPB.

Methods and analysis In this randomised controlled trial, a total of 132 patients will be recruited from the Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital. Patients will be randomised into the colchicine treatment group and control group with a ratio of 1:1. Patients in the colchicine treatment group will receive 0.5 mg of colchicine daily for 3 days before surgery and 0.5 mg of colchicine daily for 5 days after surgery. Patients in the control group will receive placebo instead of colchicine for the same schedule. Level of postoperative myocardial injury will be assessed as the primary outcome. The secondary outcomes are biomarker levels for myocardial injury (such as creatine kinase-MB, cardiac troponin I, myohaemoglobin, type B natriuretic peptide, D-dimer) and inflammatory response markers (white blood cell, procalcitonin, interleukin-6, C reactive protein) for 5 consecutive days after surgery and poor postoperative outcomes.

Ethics and dissemination This study has been approved by Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College (approval number: 2020-293-01). Study results will be disseminated through publication in an open access journal.

Trial registration number ChiCTR2000040129.

Strengths and limitations of this study

- This study is a prospective, randomised and placebo-controlled trial.
- Investigating myocardial injury of cardiac surgery according to various inflammatory biomarkers.
- This is a single-centre and single-blind trail, which could be a limitation of this study.
- The study will be limited to a Chinese population with a target schedule, and validation studies in other ethnic backgrounds will be warranted.

INTRODUCTION

Inflammatory responses and myocardial ischaemia-reperfusion injury caused by cardiovascular surgery with cardiopulmonary bypass (CPB) have been proved to be a major contributor to postoperative morbidity and mortality.[1 2] The proinflammatory response to CPB is associated with exposure of plasma proteases to the non-endothelial lining of the CPB circuit. Ischaemia-reperfusion injury during CPB, which is also an inflammatory phenomenon, is another important cause of postoperative morbidity.[3] In addition, surgery-related trauma, blood transfusion and blood loss are all important risk factors of perioperative myocardial injury.[4–6] All of these results in an inflammatory response including hormones, cytokines, chemokines, vasoactive substances, cytotoxins, reactive oxygen species and protease of the coagulation and fibrinolytic systems, will lead to myocardial injury.[7] Myocardial injury is frequently observed in patients with cardiac surgery and significantly affects prognosis.[8]

Colchicine is a classic anti-inflammatory medication that was initially extracted from the autumn crocus, which allows for safe use in patients with cardiovascular disease.[9] In the colchincine cardiovascular outcomes trial (COLCOT) study which enrolled 4745 patients recruited within 30 days after a myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischaemic cardiovascular event than placebo.[10] A pilot study also showed the potential benefit of colchicine in

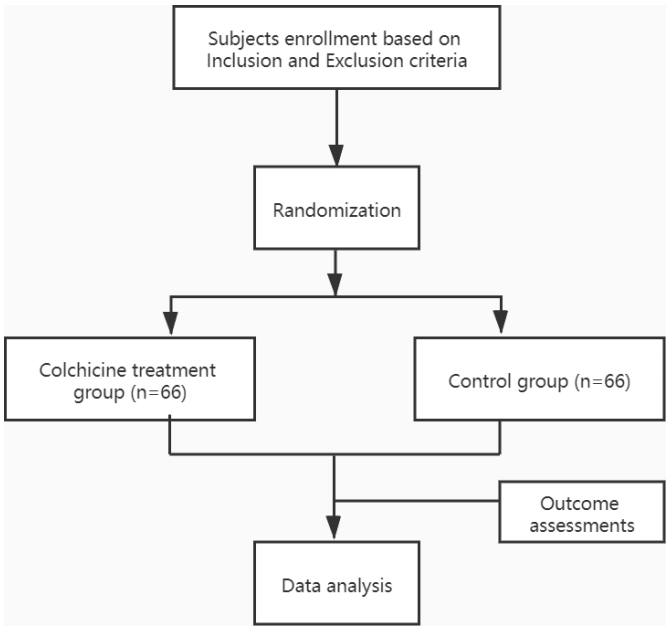

Figure 1 Flowchart of the participants through the trial.

ST-segment-elevation myocardial infarction.[11] Previous studies have shown that colchicine had a protective effect on myocardium associated with decreased interstitial fibrosis and attenuated myocardial inflammation.[12] It has been clear that colchicine could play an important role in cardioprotective effects in stable coronary disease.[13]

Giannopoulos *et al* reported a cohort of 59 patients who underwent on-pump coronary artery bypass grafting (CABG), they found that a short perioperative course of colchicine was effective in attenuating postoperative increases of hypersensitive troponin T and creatine kinase-MB (CK-MB) compared with placebo.[14] However, there were limited researches about colchicine used in patients without CABG who need valvular and aortic surgery. Therefore, we design this study to evaluate the value of myocardial protection of low-dose colchicine during perioperative course in patients who undergo cardiovascular surgery with CPB.

METHODS

Study design

This is a single-centre, single-blind, prospective, randomised controlled study (figure 1). The study began in October 2020 at the Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital. Subjects will receive colchicine or placebo for last 3 days before operation and for first 5 days after operation (0.5 mg one time per day). We anticipate that recruitment will be completed within 24 months.

Patients

Inclusion criteria

1. Adult patients undergoing on-pump cardiovascular surgery;
2. Aged 50–75 (including 50 and 75), male or female;
3. Have signed the informed consent form (ICF);
4. Patients have New York Heart Association Class I-II.

Exclusion criteria

1. Patients undergoing emergency surgery;
2. Patients undergoing deep hypothermic circulatory arrest surgery;
3. Patients with atrial fibrillation who need radiofrequency catheter ablation;
4. Patients with coronary artery disease who need percutaneous transluminal coronary intervention or CABG;
5. Poor hepatorenal dysfunction (Child Pugh Class B or C, estimated glomerular filtration rate < 35 mL/min/1.73m^2);
6. Baseline inflammatory indicators abnormal (interleukin-6 (IL-6) >10 pg/mL, procalcitonin (PCT) >0.5 ng/mL, C reactive protein (CRP) >10 mg/L);
7. Predictive mortality of European System for Cardiac Operative Risk Evaluation (EuroScore II) >3%;
8. Patients who had received cardiac surgery;
9. Patients who are diagnosed with inflammatory immune diseases;
10. Patients who received treatment of colchicine or hormone previously;
11. Patients who had history of tumour or infectious disease;
12. Patients who had colchicine allergy or intolerance;
13. Patients who receive more than 120 min of aortic cross clamp;
14. Patients who need ventricular outflow reconstruction in the surgery.

Patients will be required to provide written ICF for this research. Informed consent will require the use of clinical data and serological data during the hospitalisation.

Blinding and randomisation

Patients, outcome assessors and statisticians will be blinded. Patients in the colchicine treatment group will be given colchicine tablets, and those in the control group will be given starch tablets. We will remove the name of medicine packaging so that patients will not know which group they are in.

A research assistant who will not be involved in the study intervention and evaluation will be in charge of the randomisation. The random numbers will be generated using Microsoft Excel software in a block size of 4. Patients will be enrolled in a ratio of 1:1. Each patient will get a number according to the date when they sign the ICF.

Intervention

The treatment will start on the day the patients sign the ICF and get their randomised numbers. All patients will receive routine examinations including echocardiography, brain and chest CT, coronary arteriography (patients aged more than 50 years), laboratory tests (blood routine examination, blood biochemistry, erythrocyte

sedimentation rate, coagulation function, CK-MB, cardiac troponin T (cTnT), cardiac troponin I (cTnI), PCT, IL-6, CRP, myohaemoglobin (MYO), type B natriuretic peptide (BNP) and D-dimer). All these examinations and demographic information will be collected from the electronic medical record (EMR). Patients in the colchicine treatment group will be given colchicine 0.5 mg one time per day for the last 3 days before operation, those in control group will be given placebo for the same schedule. All patients will undergo surgery applying in-house protocol according to preoperative diagnosis. CPB and surgical information will also be recorded. All patients will be transferred to the intensive care unit after surgery and then will be removed from trachea intubation. Patients in the colchicine treatment group will be given colchicine 0.5 mg one time per day and those in control group will be given placebo 0.5 mg one time per day for the first 5 days after trachea intubation is removed. Blood samples for blood routine examination, blood biochemistry, erythrocyte sedimentation rate, coagulation function, CK-MB, MYO, BNP, D-dimer, cTnT, cTnI, PCT and IL-6 will be obtained daily for 5 days after surgery.

Outcome measures

Primary outcome

The primary outcome will be postoperative myocardial injury in the colchicine treatment group and the control group. We will assess the level of postoperative myocardial injury according to cTnT.[15] We will compare the level of cTnT continuously for 5 days after cardiac surgery between the two groups.

Secondary outcomes

The following secondary outcomes will be measured: (1) Biomarkers of myocardial injury (CK-MB, cTnI, MYO, BNP, D-dimer) levels 5 days after surgery; (2) Inflammatory biomarkers (WBC, PCT, IL-6, CRP) levels 5 days after surgery; and (3) The postoperative poor outcomes, including late prolonged mechanical ventilation (time of mechanical ventilation > 90th upper reference limit), atrial fibrillation, ventricular arrhythmias, low cardiac output syndrome, continuous renal replacement treatment, extracorporeal membrane oxygenation, intra-aortic ballon pump, etc.

Safety assessment

Colchicine has been used in clinical practice for centuries and is well tolerated. Gastrointestinal discomfort is the main adverse outcome. In the COLCOT trial, which included patients with 30 days after acute myocardial infarction (AMI), diarrhoea was reported in around 10% of patients in the colchicine group, without significant difference compared with the placebo group.[10] A rare but significantly higher incidence of pneumonia was reported as a serious adverse event in 0.9% patients in the colchicine group.[10] In the literature, colchicine treatment discontinuation has been reported in 10% of individuals.[16]

Any adverse events (AEs) during the study period will be recorded, assessed and treated. The details of AEs will be recorded in the case report form (CRF). AEs grading will be based on Common Terminology Criteria for Adverse Events V.5.0. Serious AEs will be immediately reported to Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College. The incidence of AEs will also be calculated.

Sample size calculation

Power, Analysis and Sample Size (V.11.0) was used for calculating the required sample size. This study is a parallel randomised controlled study, the level of troponin T 5 days after cardiac surgery will be the primary outcome. Preliminary measurements in patients after cardiac surgery at our institution had an average troponin T level of 0.5±0.25 μg/L in the first 48 hours. It was calculated that, colchicine treatment could detect a 30% reduction in the primary outcome measure with 90% probability (type II error probability 0.1), at an α-level (type I error probability) of 0.05, 60 subjects would have to be included in each group. Considering a dropout rate of 10%, 66 patients would be required in each group. Therefore, the sample size is 132 in this study.

Data collection and statement section

Data will be collected from EMR. CRF will be first filled in the paper copies and then entered into the Microsoft Excel by associated researchers. The original CRFs and ICFs will be kept in Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School. Data monitoring and validation will be regularly conducted throughout the study. The frequency of monitoring will be once a year by Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College, since the beginning of this study.

Statistical analyses

SPSS V.25.0 software will be used for data processing and analysis. Continuous variables will be presented as mean±SD, and counting data will be presented as number and percentage (n, %). To test the difference between two groups, t-test will be used for continuous variables following normal distribution and homogeneity of variance, otherwise we will perform Wilcoxon rank-sum test. X^2 test or Fisher's exact probability method will be used for counting data. P value <0.05 is considered to have statistical significance.

Interim analysis

Interim analysis will not be performed.

Quality control

All the researchers received Good Clinical Practice training. The concentrations of the biomarkers (PCT, CRP, BNP, cTnT, cTNI, D-dimer and IL-6) were measured by cyclic enhanced fluorescent immunoassays (CEFA) performed on a fully automated, benchtop Pylon 3D

immuno-analyzer (ET Healthcare, China) using whole blood samples. A description of CEFA assay procedures is available elsewhere.[17] In brief, the assay format is a unitised test strip containing wells with pre-dispensed reagents. A quartz-glass probe tip coated with captured antibodies moves between wells to capture the target biomarker molecules in the sample and form an immune complex with a fluorescent detection antibody. After measuring the fluorescence bound of the probe tip, the biomarker concentration is derived from a reagent lot-specific calibration curve.

All patients will undergo surgery applying in-house protocol according to preoperative diagnosis. Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College, will monitor the safety of this study and review the study results. This study will be monitored by independent Data and Safety Monitoring Board.

Patient and public involvement

Neither patients nor the public were involved in the development of the research question, choice of outcome measures, design of the trial, recruitment of participants or conduct of the trial. Results of the trial will be disseminated to study participants through direct consultation with a trial clinician at completion of the trial, as well as through the publication of results.

Ethics and dissemination

This study was approved by the Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College (approval number: 2020-293-01). All patients will be fully informed about the study and given enough time to decide whether to participate in this study. All patients will be asked to sign an ICF if they agree to participate in the study. All patients have the right to withdraw from the study at any time even though they signed the ICF. Study results will be published by an online access medical journal.

DISCUSSION

Colchicine has various anti-inflammatory effects and is widely used in inflammatory diseases. Currently, it had been well proved in cellular level and animal models that colchicine has efficacy of cardioprotection. The second low dose colchicine (LoDoCo2) study showed that colchicine could reduce the risk of cardiovascular events,[18] colchicine appears to be efficacious and well tolerated for recurrent pericarditis and postpericardiotomy syndrome and recurrence of postprocedural atrial fibrillation.[19] However, recent meta-analysis indicated that low-dose colchicine reduced the risk of major adverse cardiovascular events (MACE) as well as that of myocardial infarction, stroke and the need for coronary revascularisation in a broad spectrum of patients with coronary disease, while there was no difference in all-cause mortality and fewer cardiovascular deaths were counterbalanced by more non-cardiovascular deaths.[20] Therefore, the utility of colchicine in myocardial protection in patients with CBP is still limited and needs more randomised studies evidence.

One advantage of our study is that we will demonstrate whether colchicine has perioperative cardioprotection function in patients with CPB. Another advantage of our study is that we will provide clinical evidence about the efficacy of colchicine on patients undergoing valvular and aortic surgery. Furthermore, IL-6, PCT and CRP will be tested in this study. Therefore, this study will be used to demonstrate whether colchicine reduces systemic inflammatory in patients with CPB. It may broaden the vision of perioperative cardioprotection. We fully believe that many follow-up studies will be carried out.

According to our inclusion and exclusion criteria, this study will recruit 'low-risk' patients. However, the effect of colchicine on myocardial protection in 'high-risk' patients is unknown. We will use cTnT to evaluate the perioperative myocardial infarction. Even though cTnT has been proven to be a well-validated biomarker for postoperative outcome, it still can not be equated to a clinical endpoint. In other words, it may not improve outcome when colchicine has been proved to decrease cTnT level. The schedule of 0.5 mg colchicine still remains to be explored in Chinese people. Furthermore, some inflammatory biomarkers, including IL-10, IL-8 and tumour necrosis factor-1β, which might be useful to predict myocardial ischaemia-reperfusion injury. However, we could not test theses biomarkers. It may cause some potential inaccuracies in our study. Finally, to our best knowledge, this study is a first human-study of colchicine in patients undergoing valvular and aortic surgery. However, we removed a large number of patients who received CABG from the analysis and it may have elevated some errors.

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Contributors D-JW, TP and JP have led on design and are overseeing data analysis plans. Data management will be performed by HZ, H-TZ, KZ, Z-SL and XJ. Data quality checks will be performed by HZ and H-TZ. XH is the study statistician. HZ drafted the manuscript. The final data set will be curated by D-JW, TP and HZ, access will be at the discretion of study investigators.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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