Study Protocol and Statistical Analysis Plan

Official Title of the study: Effects of erythropoietin on acute kidney injury in patients undergoing cardiac surgery

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Acute renal injury (AKI) often occurs after cardiac surgery, while the incidence of cardiac surgery associated acute kidney injury (CSA- AKI) increases significantly in patients undergoing cardiopulmonary bypass during operation. The incidence of CSAAKI published in the current study was 8.9~39.0 %. Need of renal replacement therapy (RRT) was 1%~5% after operation, while the total mortality rate was about 1.4%. Studies have shown that even minor postoperative AKI of elevated serum creatinine was significantly associated with higher mortality. Thus, the prevention of CSA-AKI is of great importance to improve the prognosis of patients. At present, the availability of effective drugs for CSA-AKI prevention drugs is still limited.

Erythropoietin (EPO) is a kind of substance secreted by renal cortical tubulointerstitial cells and liver which is commonly used in the treatment of renal anemia. Studies have shown that EPO can prevent AKI due to the effect of potential anti-apoptotic and antioxidant. Previous documents also proved that EPO could improve renal function AKI models in rats. The safety of preoperative use has been preliminarily confirmed by some studies, but the conclusion of the effectiveness of renal protection still remains on controversial. The 2012 guidelines of AKI from Kidney Disease Improving Global Outcome (KDIGO) recommended randomized controlled studies conducted for EPO prevention of AKI. This study aimed to explore whether clinical use EPO can reduce the risk CSA-AKI in patients and improve the prognosis.

1 Object and Methods

1.1 Research subjects

All patients received non-emergency cardiac surgery in Department of Cardiothoracic Surgery, Nanjing Hospital affiliated to Nanjing First Medical University from July 2016 to May 2017.

Inclusion criteria: (1) 18 ~ 80 years old; (2) Preoperative hemoglobin < 130 g/L; (3) Surgical type: cardiopulmonary bypass, valvular or congenital heart disease surgery; (4) Signed the informed consent voluntarily.

Exclusion criteria: (1) Suffering uncontrolled infection of other sites. (2) Refused to sign the informed consent; (3) Dialysis of end stage renal disease; (4) Had the history of acute myocardial infarction, acute cerebral infarction or pulmonary embolism in recent 3 months; (5) Chemotherapy for malignant tumors; (6) Suffering uncontrolled hypertension (systolic blood pressure >200mmHg, diastolic pressure >110 mmHg). (7) Allergic to erythropoietin. (8) Administration of erythropoietin in 2 weeks before the surgery.

1.2 Research methodology

This study was a single-center randomized controlled clinical trial (RCT). For patients recruited in the study, preoperative information and some laboratory test results were collected. Patients were randomly assigned 1:1 to the EPO group and the control group using the predetermined random allocation table. The EPO group received 10000 IU of single hypodermic injection 24 hours before the operation, and the control group received equal volume of normal saline. At the same time, all subjects were followed up in hospital 7 days after the operation.

The test indicators included routine blood test, routine urine test and renal function test. Samples of blood and urine were collected at multiple time points before and after the surgery to detect early indicators of renal injury and inflammation. Including neutrophil Gelatinase associated lipocalin (NGAL), interleukin (IL-18), urinary kidney injury molecule-1 (KIM-1), C-reactive protein (CRP), IL-6, etc. Other clinical index such as occurrence of postoperative AKI, length of hospital stay, intensive care unit stay time, renal replacement therapy (require renal replacement therapy), death, acute physiology and chronic health evaluation (APACHE II) score, lung infections, etc. were collected.

The diagnosis of AKI after cardiac surgery was based on the 2012 KDIGO AKI Guidelines. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing First Hospital (KY20160721-02).

1.3 Statistical methods

SPSS (V22.0, SPSS, Inc., Chicago, IL, USA) and Graphpad Prism 8.0 software were used for data analysis. Continuous data subject to normal distribution were expressed as mean ± standard deviation, and the independent sample T-test was used to compare the difference of the mean between the two groups. Repeated measurement design ANOVA was used to compare the differences between different groups at multiple time points. The categorical variables were presented as number (%) and compared by Pearson chi-square test.