An Adjusted Calculation Model of Reduced Heparin Doses in Cardiopulmonary Bypass Surgery in a Chinese Population

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Objective: **To investigate the safety and efficacy of an adjusted regimen of heparin infusion in cardiopulmonary bypass (CPB) surgery in a Chinese population.**

Design: **Prospective, single-center, observational study.**

Setting: **University teaching hospital.**

Participants: **Patients having cardiac surgery with CPB were selected for this study using the following criteria: 18 to 75 years of age, undergoing first-time cardiac surgery with conventional median sternotomy, aortic clamping time between 40 and 120 minutes, and preoperative routine blood tests showing normal liver, renal, and coagulation functions. The exclusion criteria include salvage cases, a history of coagulopathy in the family, and long-term use of anticoagulation or antiplatelet drugs.**

Interventions: **Sixty patients were divided randomly into a control group (n = 30) receiving a traditional heparin regimen and an experimental group (n = 30) receiving an adjusted regimen.**

Measurements and Main Results: **Activated coagulation time (ACT) was monitored at different time points, ACT >480 seconds was set as the safety threshold of CPB. Heparin doses (initial dose, added dose, and total dose), protamine doses (initial dose, added dose, and total dose), CPB time, aortic clamping time, assisted circulation time, sternal closure time, blood transfusion volume, and drainage volume 24 hours after surgery were recorded. There was no significant difference in achieving target ACT after the initial dose of heparin between the 2 groups; CPB time, aortic clamping time, assisted circulation time, postoperative complication rate, and drainage volume between the 2 groups were not significantly different ($p > 0.05$). However, initial and total dosage of heparin, initial and total dosage of protamine, sternal closure time, and intraoperative blood transfusion volume in the experimental group were significantly lower ($p < 0.05$).**

Conclusions: **Adjusted regimen of heparin infusion could be used safely and effectively in Chinese CPB patients, which might reduce the initial and total dosage of heparin and protamine as well as sternal closure time and intraoperative blood transfusion volume.**

KEY WORDS: individual administration, heparin, activated clotting time, cardiopulmonary bypass, transfusions, protamine, anticoagulation

THERE IS NO COMMONLY recognized regimen for heparin infusion in cardiac surgery with cardiopulmonary bypass (CPB).[1] Heparin inadequacy could lead to failure of CPB or even thromboembolic events, whereas heparin overdose could cause excessive blood loss during sternal closure.[2] In addition, rapid administration of protamine, used to neutralize excessive heparin, could cause life-threatening hemodynamic disturbance, along with histamine release and hypoxemia, especially at the end of CPB.[3] Additional use of protamine after CPB also could increase allergy risks and bleeding.[4] Currently, 300 IU/kg is used widely as the initial dosage of heparin administered before starting CPB. Activated coagulation time (ACT) is used as an indicator of the effectiveness of heparin intraoperatively, with ACT >480 seconds as the safety threshold of CPB.[5,6] In this regimen, heparin dosage calculation is based solely on patient body weight. The regimen may achieve target ACT quickly but often causes heparin overdosing. Moreover, heparin rebound after CPB may require additional protamine administration,[7] especially in Chinese populations.

Adjusted heparin regimens have been used in some research projects,[8,9] but most subjects in these studies were European and American. According to the experience of the authors there are more bleeding than embolism events in Chinese populations during the process of anticoagulation compared with European and American populations.[10,11] The hypothesis in the present study was that less heparin is needed in cardiac surgeries for Chinese people. Recently, Nakasuji et al developed an original formula, which had been proven effective to calculate the initial dose of heparin[12]; this formula takes into account baseline ACT (bACT) and body weight. In the present study, bACT and target ACT >480 seconds were taken into account to develop an adjusted formula. The main objective of the present study was to evaluate the safety and effectiveness of this adjusted formula in CPB.

MATERIAL AND METHODS

Patients who underwent cardiac surgery with CPB from January 2013 to December 2014 in the Department of Cardiothoracic Surgery in Changzheng Hospital were selected.

Inclusion criteria were as follows: 18 to 75 years of age, undergoing first-time cardiac surgery with conventional median sternotomy, aortic clamping time between 40 and 120 minutes, and preoperative routine blood tests showing normal liver, renal, and coagulation function.

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Table 1. Preoperative Baseline Characteristics

Groups	Control Group (n = 30)	Experimental Group (n = 30)	p Value
Age (year)	55.90 ± 12.75	52.80 ± 11.15	0.75
Sex (male)	16	14	0.606
Height (cm)	162.10 ± 10.09	163.63 ± 9.25	0.54
Weight (kg)	58.10 ± 10.69	61.33 ± 10.65	0.24
Heart function (NYHA)			
Class II	13	12	0.793
Class III	12	14	0.602
Class IV	5	4	0.718
Diabetes	4	6	0.488
Hypertension	6	8	0.542
COPD	6	4	0.488
Preoperative Hb (g/L)	11.85 ± 1.22	11.69 ± 1.04	0.58
Preoperative Hct (%)	34.90 ± 3.59	34.59 ± 3.41	0.73
Preoperative platelet Count (c/mL)	192.67 ± 52.76	181.07 ± 51.31	0.391

NOTE. Values expressed as number, median (interquartile range), or mean ± standard deviation.

Abbreviations: NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; Hct, hematocrit value.

Exclusion criteria were: salvage cases, a history of coagulopathy in the family, and long-term use of anticoagulation or antiplatelet drugs due to atrial fibrillation, cerebral infarction, or unstable angina. All included patients signed informed consent forms meeting ethical standards of the Human Research Committee of Changzheng Hospital. All surgeries were performed by the same group of surgeons, anesthesiologists, and perfusionists.

Groups

With an alpha value of 0.05 and a desired power of 0.80, it was found that 27 participants were required for each group to address the primary aim of the study. The authors planned the study with 30 patients in each group. A total of 60 patients were enrolled and randomized into a control group (n = 30) and an experimental group (n = 30). A traditional regimen, with initial dose of heparin (units) = body weight (kg) × 300 U/lg, was used in the control group. An adjusted regimen, with initial dose of heparin (units) = Body weight (kg) × 300 U/kg × (480 – bACT) / (480 –100), was used in the experimental group. Patients' general information included name, sex, age, body weight, hospitalization number, and diagnosis. Perioperative states of heart, lung, liver, kidney, and coagulation function and information regarding history of diabetes or hypertension also were collected. Surgery information included the type, mode, and date of surgeries. Surgeons, anesthesiologists, and caregivers were blinded to this information.

Anesthesia and Cardiopulmonary Bypass

Anesthesia was induced with 0.1 mg/kg of midazolam, 1 to 2 μg/kg of sufentanil, and 0.2 mg/kg of vecuronium, and it was maintained with propofol, sufentanil, and vecuronium. Electrocardiogram, arterial pressure, central venous pressure, pulmonary artery pressure, and cardiac index, as well as nasopharyngeal temperature, rectal temperature, and blood gas were monitored during the procedure.

The circuit was primed with 1,000 mL of gelatin solution, 500 mL of Ringer's acetate, 400 mL of mannitol, 160 mg of sodium chloride, and 2000 U of heparin. Myocardial protection was achieved by using cold (4°C) crystalloid cardioplegia solution (St. Thomas Hospital cardioplegic solution No. 2; Plegisol W, Abbott Laboratories, Chicago, IL). The targeted mean perfusion pressure was 50 to 70 mmHg. Patient temperature was maintained between 34°C and 36°C, and blood flow was kept between 2.2 and 2.4 L/min/m^2. A cell-saving device was used to process red blood cells during the whole procedure.

The initial dose of heparin was administered according to 2 different regimens. ACT was measured 4 times before administration of heparin, and bACT was the mean of 4 numeric values. If required, additional doses of heparin (5000 U) were administered during CPB to maintain an ACT >480 seconds. After termination of CPB, heparin was antagonized with protamine at a 1:1 ratio, and then ACT was measured to exclude residual heparin. Blood was transfused to maintain hemoglobin >7g/L and hematocrit >0.20.

Evaluation of Adjusted Regimen

ACT was monitored at 5 different time points, including T0 (before heparin infusion), T1 (3 minutes after initial heparin infusion), T2 (30 minutes after CPB), T3 (before protamine administration), and T4 (5 minutes after protamine administration).

Initial, additional, and total dose of heparin and protamine; CPB time; aortic clamping time; assisted circulation time; sternal closure time (from termination of CPB to termination of surgery); blood transfusion volume; and chest drainage volume were recorded.

Statistical Methods

Categorical variables are presented as the number of observations. Continuous variables are presented as the mean - ± standard deviation. Statistical analysis was performed with the IBM SPSS 19 (SPSS, Inc, Armonk, New York). Data were compared by using one-way analysis of variance and χ^2 test; p values < 0.05 were considered significant.

Table 2. Comparison of Surgery Types Between the 2 Groups

	Control Group (n = 30)	Experimental Group (n = 30)	p Value
MVR + TVP	12	14	0.602
AVR	8	6	0.542
MVR + AVR + TVP	4	5	0.718
TVP	1	2	0.554
ASD/VSD	5	3	0.448

NOTE. Values expressed as number.

Abbreviations: MVR + TVP, mitral valve replacement and tricuspid valvuloplasty; AVR, aortic valve replacement; MVR + AVR + TVP, mitral valve replacement, aortic valve replacement, and tricuspid valvuloplasty; TVP, tricuspid valvuloplasty; ASD, atrial septal defect; VSD, ventricular septal defect.