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Efficacy of Autologous Plateletpheresis in Adult Aortic Surgery: Study Protocol for a Randomised Controlled Trial

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Abstract (250 words)

Introduction Perioperative coagulopathy is common in patients undergoing aortic surgery, increasing the risk of excessive blood loss and subsequent allogeneic transfusion. Blood conservation has become a vital part of cardiovascular surgery, but measures to protect platelets from destruction by cardiopulmonary bypass (CPB) still are lacking. Autologous platelet concentrate (APC) may have potential benefits for intraoperative blood preservation, but its effectiveness has not been studied extensively. This study aims to evaluate the effectiveness of APC as a blood conservation technique to reduce blood transfusion in adult aortic surgery.

Methods and analysis This is a prospective, single-center, single-blind randomized controlled trial. A total of 344 adult patients undergoing aortic surgery with CPB will be enrolled and randomized to either the APC group or the control group with a 1:1 randomization ratio. Patients in the APC group will receive autologous plateletpheresis

before heparinization, while those in the control group will not. The primary outcome is the perioperative packed red blood cell (pRBC) transfusion rate. Secondary endpoints include the volume of perioperative pRBC transfusion; drainage volume within 72 hours post-surgery; postoperative coagulation and platelet function; and the incidence of adverse events. Data will be analyzed according to the intention-to-treat principle.

Ethics and dissemination This study was approved by the institutional review board of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (**No.2022-1806**). All procedures included in this study will be performed in adherence to the Helsinki declaration. The results of the trial will be published in an international peer-reviewed journal.

Trial registration number Chinese Clinical Trial Register (ChiCTR2200065834)

Key words plateletpheresis; aortic surgery; transfusion

Strengths and limitations of this study:

1. This will be a randomized controlled trial aimed at evaluating the efficacy of autologous plateletpheresis in adult patients undergoing aortic surgery, which will provide important implications.
2. The use of the autologous plateletpheresis method in this study is a novel approach that has not been previously investigated, and the primary and secondary outcomes are strong clinical outcomes pertinent for patients. The study will also provide valuable information on potential benefits for individuals and the healthcare system.
3. This will be a single-center trial, which can be a limitation of this study.
4. This study will exclude some high-risk populations, including juveniles, adults over the age of 65, and individuals undergoing thoracoabdominal aorta replacement, under the consideration of heterogeneity.

INTRODUCTION

Aortic surgery is associated with increased bleeding. Consumption and dilution of coagulation factors, activation of the systemic inflammatory response and fibrinolysis, ischemia-reperfusion injury, surgical trauma, usage of deep hypothermic circulatory

arrest (HCA), and acquired thrombocytopenia and thrombocytopathy resulted by prolonged cardiopulmonary bypass (CPB) lead to perioperative coagulation disorders, which increases the risk of excessive blood loss and subsequent allogeneic transfusion. Studies have shown that platelet concentrate (PC) transfusion is the first line treatment for assumed hemostatic impairment[1, 2], and in adult patients with active bleeding, a single unit of platelets is expected to increase platelet count by an average of $15\text{-}25\times10^9$ /L[1].

According to the data of Fuwai Hospital in 2013, the annual perioperative PC transfusion rate in cardiovascular surgery was 11.67%. The highest rates of PC transfusion were observed in patients undergoing descending thoracic aorta replacement (100%) and total aortic arch replacement and stented elephant trunk implantation (91.49%). Furthermore, the average PC transfusion volume administered to patients was (1.53±1.20) units, with the largest average volume being administered to patients undergoing thoracic descending aorta replacement was (3.07±1.59) units. However, allogeneic transfusion is associated with an increased rate of postoperative pulmonary complications, infections, transfusion-related circulatory overload, prolonged mechanical ventilation duration, prolonged hospital length of stay, total hospitalization cost, and an increase in in-hospital mortality in patients undergoing aortic surgery[3]. Recent research found that transfusion of packed red blood cells (pRBC), fresh frozen plasma (FFP), or PC is associated with mortality and infection after cardiac surgery in a dose-dependent manner[4]. Therefore, blood conservation has become a vital part of cardiovascular surgery.

The implementation of patient blood management (PBM) in cardiac surgery, which includes correcting preoperative anemia, reducing intraoperative hemodilution, and administering antifibrinolytic drugs, has been demonstrated to be a safe and effective approach to reduce allogeneic blood transfusion, improve clinical outcomes, and conserve blood resources[5-8]. Moreover, autologous pre-donation of blood products, blood salvaging systems, cell saver techniques, minimized pump prime, pharmacologic agents, and autologous reinfusion have been demonstrated to confer advantages. However, measures to protect platelets from destruction by CPB still are

lacking. Autologous platelet-rich plasmapheresis (APP) is a novel method of autologous blood transfusion. In this procedure, whole blood is collected into a citrate-treated bag via the central vein and then centrifuged at a rate of 2,400 to 3,500 rpm in a platelet separation device. This centrifugation separates the whole blood into RBCs, platelet-poor plasma (PPP), and platelet-rich plasma (PRP) based on specific gravity. This technique has been found to effectively protect platelets from damage and has been utilized in cardiovascular surgery[8-11]. A recent clinical trial has demonstrated that the utilization of APP results in a 34% decrease in pRBC transfusion rate, a 52.8% decrease in FFP transfusion rate, and a 56.7% decrease in PC transfusion rate, along with a decrease in hospitalization duration and costs associated with blood transfusion[9]. However, conflicting results have been reported regarding the use of APP in cardiac surgery as it is unclear whether this harvest process is associated with hemodynamic instability, which could potentially lead to organ ischemia[12]. Autologous platelet concentrate (APC) is characterized by a higher platelet count than aPRP, and its harvest process has a minimal impact on hemodynamics. We hypothesized that the use of APC produced through autologous plateletpheresis can reduce perioperative allogeneic blood transfusion in patients undergoing aortic surgery without any impact on perioperative adverse events. To verify our hypothesis, we designed a randomized controlled trial to investigate the efficacy of autologous plateletpheresis in adult aortic surgery.

METHODS AND ANALYSIS

Study setting and trail design

This study has been approved by the Ethics Committee of Fuwai Hospital (**No.2022-1806**) and has been registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn/), with the registry number ChiCTR2200065834.

It is a prospective, single-center, and single-blind randomized controlled trial that will enroll eligible adult patients undergoing aortic surgery with CPB, who have given their informed consent to participate. The patients will be randomly assigned in a 1:1 ratio to either the APC or control group. The APC group will undergo autologous

plateletpheresis before heparinization, whereas the control group will not. To ensure the blinding of the study, the intensive care unit (ICU) staff, nurses, outcome assessors, data collectors, and data analysts will not be aware of the patient grouping.

Data will be collected after central venous catheterization (T0), before heparinization (T1), end of surgery (T2), 24 hours post-surgery (T3), 48 hours post-surgery (T4), and 72 hours post-surgery (T5) until discharge. The data will be presented following SPIRIT checklist[13] and analyzed according to the intention-to-treat principle. The study flowchart is shown in figure 1.

Study population

We plan to enroll 344 adult patients who are scheduled to undergo aortic surgery with CPB at Fuwai Hospital in Beijing, China. Eligible participants must meet the following inclusion criteria: (1) diagnosis of aortic disease (including aortic aneurysm, aortic dissection, and aortic coarctation) and scheduled for elective cardiac surgery with CPB, (2) American Society of Anaesthesiologists (ASA) classification I-III, (3) adult patients aged 18-65 years, with a weight of over 50 kg, (4) platelet counts over 150×10^9/L, (5) willingness to provide informed consent for participation in the study.

Patients who present with any of the following exclusion criteria will not be eligible for enrollment: (1) history of platelet donation within 15 days prior to surgery, (2) preoperative cardiogenic shock, cardiac arrest, severe systolic hypotension, oxygen saturation of mixed venose blood (SvO_2) < 75%, on mechanical circulatory support, (3) thrombocytopenia, platelet dysfunction (as diagnosed by thrombelastogram platelet mapping) or any other known history of a bleeding disorder, (4) thromboembolic disease (such as pulmonary embolism, spontaneous arterial thrombosis, or familial hypercoagulability), (5) intellectual or legal disabilities, (6) severe renal impairment (serum creatinine level of >3.3 mg/dL), (7) stroke (history/acute), (8) vitamin K and/or vitamin C deficiency, (9) allergy or contraindication to citrate anticoagulants or its components, (10) breastfeeding or pregnancy, (11) trauma with multiple organ injury, and (12) current enrolment in another perioperative interventional study.

Randomization and blinding

The participants in this study will be divided into two groups, the APC group and the control group, using a computer-generated random number sequence. The participants will be assigned to each group in a 1:1 ratio using simple randomization. The results of the randomization will be kept confidential and stored in envelopes with a 5-digit randomization number written on the cover. The envelopes will be opened in sequential order according to the participant's selected time, to determine the group assignment. To minimize potential bias, the operators and evaluators will be selected from different physician teams. The anesthesiologist will be informed of the participant's group assignment after endotracheal intubation, as the intervention requires their cooperation. The study design is single-blind, as the surgeon, ICU staff, nurses, outcome assessors, data collectors, and data analysts will be unaware of the participant's group assignment.

Anesthesia induction and maintenance

The patients selected for the study received a standardized anesthesia method. Vital signs will be monitored through Electrocardiogram (ECG), oxygen saturation (SpO_2), and invasive blood pressure through the left radial artery/brachial artery and left dorsalis pedis artery/femoral artery when entering the operating room. Baseline measurements of hemodynamic parameters will be obtained by measuring and recording Bispectral index (BIS) and regional cerebral oxygen saturation ($rScO_2$). Induction of intubation will be facilitated with a combination of midazolam (0.05-0.1 mg/kg), etomidate (0.2-0.3 mg/kg), sufentanil (0.5-1 μg/kg), and cisatracurium (0.2 mg/kg). A protective ventilation strategy will be employed, with a tidal volume (VT) of 6-7 ml/kg, Positive end-expiratory pressure (PEEP) of 4-8 mmHg, Fraction of inspiration O_2 (FiO_2) of 0.5-1.0, and ventilation rate adjusted to maintain an end-tidal partial pressure of carbon dioxide ($PETCO_2$) at 35-45 mmHg. Body temperature will be monitored through the nose and rectum. The dosages of propofol, dexmedetomidine, and sevoflurane will be adjusted to maintain a BIS between 40 and 60, with BIS≤10 during deep hypothermic circulatory arrest (DHCA). Intermittent administration of

sufentanil (0.5-1.0 μg/kg) and cisatracurium (50μg/kg) will be performed. After intubation, both groups received an 8.5Fr three-lumen central venous catheter and an 8.5Fr Swan-Ganz catheter through the right internal jugular vein. Blood transfusion is strictly supervised and follows the indication of blood transfusion published by our center[14]. Standardized intraoperative blood conservation techniques, cell-salvage and pump suction will be used in both groups.

Interventions

After induction of general anesthesia, the platelet separation device (Fresenius Kabi, COM.TEC, equipped with disposable separator pipeline consumables of Fresenius C5L) will be connected to the central vein and Swan-Ganz catheter. The process will be initiated by entering the patient's demographic data including gender, height, weight, hematocrit, platelet count and blood collection rate (usually in the range of 50-80 mL/min) via the Menu key on the device. A balanced salt solution (Ringer's lactate solution) or 9% normal saline is used to maintain vascular volume and hemodynamic stability. The collection should be completed before heparinization. The harvested APC will be stored in citrate-treated bags, kept at room temperature and maintained through oscillation for a maximum of 6 hours, then reinfused to the patient after reversal of heparin. The duration of the whole process for each therapeutic dose typically ranged from 25 to 60 minutes.

Endpoints and definitions

The primary endpoint of the study is the rate of pRBC transfusion during the perioperative period. Secondary endpoints include the volume of perioperative pRBC transfusion; drainage volume; and the incidence of adverse events (major bleeding, re-operation, myocardial infarction, stroke, acute kidney injury, pulmonary insufficiency, postoperative infection, and early mortality). Additionally, other study variables will be mechanical ventilation duration; intensive care unit stay; hospital length of stay; postoperative coagulation, platelet function and the direct cost of transfusions.

Perioperative transfusions are defined as all transfusions given intraoperatively

and within 72 hours of the surgery's end time. This included a period of more than 72 hours in cases of delayed closure. Drainage volume is defined as the volume of fluid collected from pericardial and mediastinal drainage tubes within 72 hours after surgery. Major bleeding is defined as bleeding resulting in death, reoperation due to bleeding, intracranial hemorrhage, transfusion of 5 or more units of pRBCs over 48 hours, or pericardial and mediastinal tube drainage exceeding 2000 mL over 24 hours. Re-operation is defined as excessive chest tube drainage and/or pericardial tamponade requiring re-operation. Myocardial infarction will be diagnosed based on the development of pathological Q waves on two or more adjacent leads on an ECG, changes indicative of ischemia (ST-segment elevation or depression) on an ECG, and/or a change in the serum level of creatine kinase-muscle/brain of more than 75 µg/L. Stroke will be diagnosed based on the presence of a prolonged (72 hours) or permanent neurological deficit (such as paralysis, weakness, or speech difficulty) that is associated with abnormal results on magnetic resonance imaging or computed tomography scans[15]. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network[16]. The change in renal function will be assessed based on the ratio of the peak serum creatinine level to the preoperative serum creatinine level. A patient will be considered to have mild AKI if the highest ratio is between 1.5 and 2.0, moderate AKI if the highest ratio is between 2.0 and 3.0, and severe AKI if the serum creatinine level is ≥4.0 mg/dL, peak ratio is >3.0, or renal replacement therapy is required. Pulmonary insufficiency will be diagnosed based on the presence of prolonged ventilator support of more than 24 hours, the development of acute respiratory distress syndrome, pulmonary edema, pneumonia, or reintubation. Postoperative infection will be diagnosed based on the presence of clinical signs such as fever, radiographic findings such as new infiltration on chest X-rays or computed tomography scans, positive microbiological culture of an endotracheal aspirate ($\geq 10^6$ colony forming units/mL) or bronchoalveolar lavage ($\geq 10^4$ colony forming units/mL), and leukocytosis. Early mortality is defined as all-cause mortality within 30 days of the index procedure[15]. The direct cost of transfusions is defined as the charge to the hospital by the blood banking service for the blood product transfusions only, and does

not include the cost of administering the transfusions.

Sample size estimation

The sample size calculation will be based primarily on the incidence of perioperative pRBC transfusion rate. According to the data from adult aortic surgeries performed at Fuwai Hospital in 2019, a total of 326 cases of aortic surgery were performed, of which 236 cases received pRBC transfusion. According to the results of previous studies[9, 11], to ensure sufficient detection power, it was estimated conservatively that the perioperative pRBC transfusion rate in the APC group could be reduced by 15% compared to the control group, that is, from 72.39% to 57.39%. The sample size was calculated to be 310 patients, considering a significance level of $\alpha = 0.05$, a power of 0.80, and randomization in a 1:1 ratio. Accounting for potential crossovers, protocol violations, and a 10% loss-to-follow-up rate, 344 patients were expected to be enrolled in the clinical trial.

Statistical analysis

The data collected from the study will be analyzed and presented following the Consolidated Standards of Reporting Trials guidelines, following the intention-to-treat principle. Based on sample size calculation and 10% loss to follow-up, 344 patients will be included (assuming a two-tailed 5% type I error rate and 80% power) and randomized to either the APC group or the control group. One's randomization number will be reserved while the procedure is canceled for some special circumstances. The patient will be excluded and an extra random number will be generated to enroll enough patients to the preset sample size if he/she does not undergo surgery until the end of the trial.

Normal distribution of continuous variables will be tested using the Shapiro-Wilks test. To ensure consistency, continuous variables will be presented as mean ± standard deviation if the variables follow a normal distribution, otherwise median and interquartile range (IQR), categorical variables will be presented as numbers and percentages. Missing data will be managed via multiple imputations. Continuous

variables with normal distribution will be compared by Student's t-test between two groups. Continuous variables with skewed distribution will be compared by Mann-Whitney U test. We will compare categorical variables with the $\chi 2$ test or Fisher's exact test. The Spearman rank correlation test will be utilized to assess the correlation between continuous variables. Regression analysis will be performed if the differences in baseline characteristics between the two groups are statistically significant. A logistic regression model will be used to analyze pRBC transfusion exposure and the outcome events. If the outcome event proved to be rare, a Poisson regression model was used. The outcomes will be presented as a percentage with 95% CI. Sensitivity analysis will include a complete case. After half of the study participants have completed the trial, an interim analysis will be conducted to assess efficacy. The study will be terminated (stopped early) if any of the following occurs: i) The study hypothesis cannot be proved after study completion based on the current findings: the conditional power is less than 80% even if the remaining 50% of total sample size is enrolled; ii) The study violates the ethical standards for obvious safety concerns (such as increased risk in adverse events). Subgroup analyses of the primary and secondary outcomes will be performed based on important patient clinical characteristics, results will be expressed as risk differences.

The analysis will be performed by a dedicated data analyst who is masked to the subjects' group allocation. All the tests in the present study are two-tailed and $P<0.05$ is considered statistically significant.

Data management and quality control

In this study, a well-designed case report form will be used to collect baseline characteristics of eligible patients. Two to three individuals will be trained to assist in the collection of baseline characteristics, including demographic data and medical history. Laboratory test results will be obtained from a digital medical record system. A dedicated person will record all data in an Excel spreadsheet, with any data containing personal and sensitive information stored separately. Statistical analysts will only be able to see de-identified data that does not include any sensitive information.

Access to the Excel spreadsheet will be restricted until the statisticians analyze the collected data after the study. All paper documents are kept in a secure filing cabinet at Fuwai Hospital and must be kept for at least 15 years after the study is completed. After this period, any documents must be discarded with the consent of Fuwai Hospital.

All participants in this trial, including surgeons, anesthesiologists, ICU staff, nurses, outcome evaluators, data collectors, and data analysts, will receive uniform training to be familiar with the detailed procedures of the trial before the enrollment of the first patient. The Clinical Trial Steering Committee is composed of the chief supervisor and five members who have over five years of clinical trial experience. The committee is responsible for organizing biweekly meetings to address any trial-related issues and oversee the conduct and progress of the trial. Five commissioners will coordinate the work of relevant departments and provide necessary support to the trial.

Patient and public involvement

In our study, we prioritize the active involvement of patients, anesthesiologists, ICU staff, nurses, and surgeons from the early stages and throughout the study to ensure their comprehension and endorsement of the study results. During the study design phase, we consulted with five hospitalized patients scheduled to undergo aortic surgery. These individuals provided invaluable feedback on recruitment strategies, timing of data collection, and participant communication. This engagement helped to ensure that the study design was centered on the needs of patients. Moreover, involving patients and patient organizations will be essential for disseminating the trial's results to the wider public.

Study status

The trial enrolled its first patient in November 2022 and is scheduled to end in December 2024. As of the time of manuscript submission, 10 participants have been enrolled in the study.

DISCUSSION

This is currently the first randomized controlled trial to evaluate the efficacy of autologous plateletpheresis in adult patients undergoing aortic surgery. The autologous plateletpheresis method we will perform in this study is a novel approach that has not been previously investigated, which will provide important implications for adult cardiac surgery. We hypothesized that the use of APC produced through autologous plateletpheresis can reduce perioperative allogeneic blood transfusion in patients undergoing aortic surgery without any impact on perioperative adverse events.

Perioperative coagulopathy and bleeding are common complications in cardiovascular surgery with CPB and result in an increased rate of allogeneic blood transfusion. Complex aortic surgery, in particular, is often performed with DHCA, which plays a key role in cerebral protection[17, 18]. Nonetheless, aortic surgery with DHCA is strongly linked with prolonged CPB time, deep hypothermia, and excessive consumption of coagulation factors, which increase the likelihood of requiring allogeneic blood products[19]. Establishing a reasonable PBM program may be an effective strategy for conserving blood resources in these populations.

Cardiac surgery with CPB often is associated with low platelet counts and platelet dysfunction[20, 21]. Platelets have been extensively studied for their crucial functions in maintaining vascular integrity to prevent spontaneous hemorrhage and for primary hemostasis, which involves the cessation of bleeding upon vascular injury[22]. Following injury, platelets interact with various adhesive proteins of the exposed subendothelium through membrane glycoprotein (GP) receptors, including integrins, immunoglobulin-like receptors and the leucine-rich repeats of the GPIb-V-IX complex, resulting in platelet adhesion. This adhesion allows for the interaction of GPVI with collagen, which initiates platelet activation and the release of δ-granule contents, such as adenosine diphosphate, adenosine triphosphate and serotonin, and the synthesis of thromboxane A2[22]. These soluble secondary agonists, together with thrombin generated at the site of injury, contribute to further platelet activation, resulting in the binding of soluble fibrinogen to the activated αIIbβ3 integrin and the formation of a platelet-fibrin plug that seals the breach and stops bleeding[23]. Platelet transfusion is therefore the primary therapy for patients with thrombocytopenia or platelet

dysfunction who require procedures or surgery.

Although allogeneic platelet transfusion can effectively improve coagulation function, it may not be an adequate solution to this problem due to the risks associated with massive allogeneic blood transfusion. Autologous blood transfusion was long considered safer on the ground of immunization and viral risks, as it reduces the exposure to various donors[23, 24]. In 1977, Harke and colleagues[25] first reported the use of APP in cardiac surgery. Then in 1987, Ferrari et al[26] performed perioperative plasmapheresis to collect aPRP and demonstrated a reduction in blood loss and the need for allogeneic blood transfusion. Since then, APP has been widely used in cardiovascular surgery because it sets aside a subset of the patient's own platelets from the circulation during surgery and prevents exposure of that platelet subset to the CPB circuit, decreasing the risk of global platelet dysfunction[8, 9, 27]. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recommended in 2011[28] indicating that APP may be a reasonable approach to support blood conservation strategies in high-risk patients if an adequate yield can be reliably obtained (Class IIa, Level of Evidence A). However, the results of these studies are not consistent. Van et al[29] demonstrated that APP can reduce neither perioperative blood transfusions nor blood loss. Triulzi et al[30] found that APP reduced postoperative blood loss, but there was no significant reduction in perioperative allogeneic blood transfusions, so they did not support the use of APP in low-risk cardiac surgery. Since then, the use of APP has declined gradually, as their effectiveness and applicability have been controversial. The volume of blood collected for obtaining sufficient platelets is around 20-30% of the total blood volume, potentially resulting in circulatory instability and aggravate hemodilution due to fluid overload.

In comparison to the traditional APP process, the autologous plateletpheresis method implemented in this trial did not require the extraction of a large volume of whole blood, but rather utilized an external circulation to sustain a stabilized quantity of isolated blood of approximately 170 ml, thereby avoiding excessive hemodilution and circulatory instability. The efficacy of PC transfusions in hemostasis depends on the achievement of both platelet count and clot quality[2, 31, 32]. Current study[33]

demonstrates that the APC procedure does not result in platelet dysfunction. Furthermore, APC usually contains 3-4 $\times 10^{11}$ platelets in approximately 300 ml of plasma, which is significantly higher than PC. Transfusion of one APC unit will raise the platelet count by approximately 30×10^{3}cells/μl[34], which seems to be a more effective hemostatic approach in cardiovascular surgery. Moreover, the patient selection process will be based on widely accepted platelet donation criteria. Patients with preoperative platelet counts ranging from 150-450*10^{9} /L will be included, as a low platelet count before surgery may increase the risk of intraoperative hemorrhage, while a high platelet count may indicate an underlying disease or a higher risk of thrombosis[35]. Hence, this study ensures a high level of safety.

LIMITATIONS

Our trial has certain limitations that need to be acknowledged. Firstly, this will be a single-center trial so the result may not be generalizable to all centers due to some inevitable confusion, thus a multi-center study with a large sample size will be needed in the future. Secondly, research has shown that females have a higher rate of pRBC transfusions than males due to lower RBC counts, Hb levels, and circulating blood volume. As this study includes a wide range of patients, there may be differences in baseline characteristics, such as gender, and multivariate correction will be utilized in statistical analysis to mitigate potential bias[36-39]. Additionally, patients undergoing aortic surgery in our center tend to have more complex diseases, leading to increased postoperative transfusion requirements compared to other centers. Therefore, this study will exclude high-risk populations, including juveniles, adults over the age of 65, and individuals undergoing thoracoabdominal aorta replacement, to account for heterogeneity.

CONCLUSIONS

This study is a prospective, randomized controlled trial, conducted at a single center and will be the first to evaluate the efficacy of autologous plateletpheresis in adult aortic surgery. The findings from this study will have important implications for adult aortic

surgery and may potentially introduce a new approach for perioperative blood conservation strategy in patients undergoing cardiovascular surgery.

Contributors JG and HJ conceived the study and initiated the study design. JG, JJ, XG and HJ will be involved in study implementation. JG provided statistical expertise in clinical trial design and will conduct the statistical analysis. JJ, XG and HJ will provide expertise with data interpretation. All authors participated, read and approved the final manuscript.

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Data statement The final trial data for this protocol could be supplied on reasonable request.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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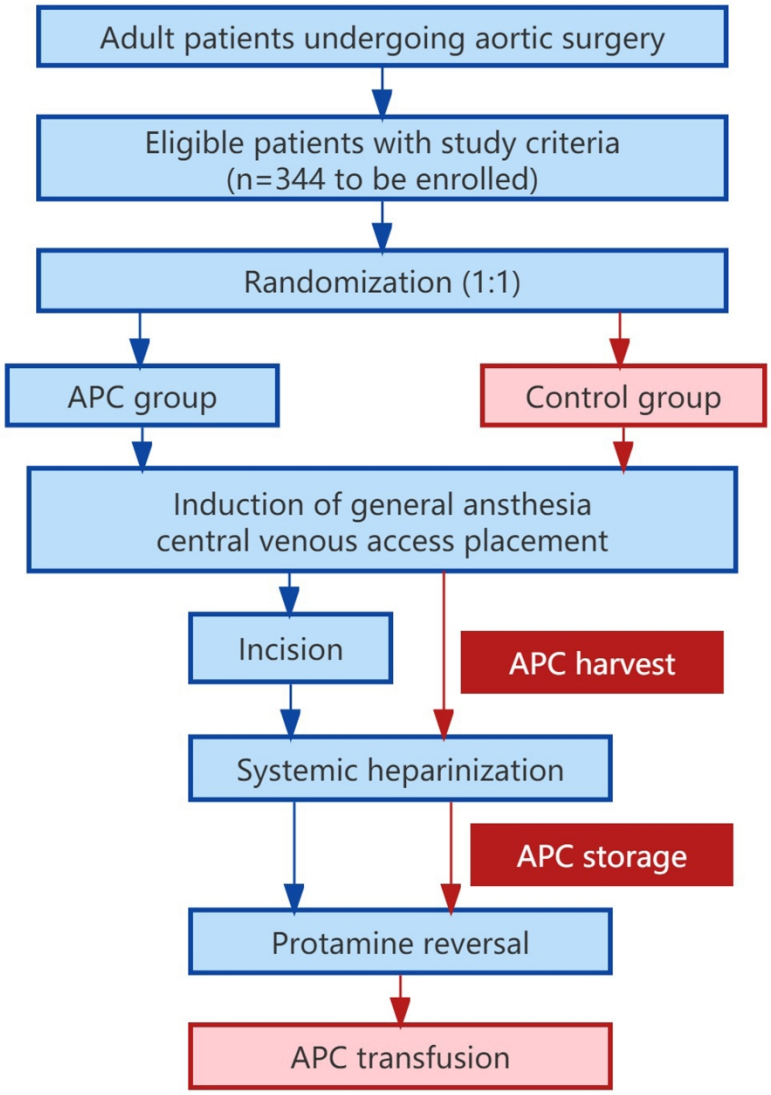
Figure 1. Flowchart of the study. The flowchart depicts the participant timeline and trial design, commencing from participant enrollment and subsequent allocation to either the APC group or control group, and concluding with perioperative management of both groups. APC, Autologous platelet concentrate.



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385x526mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-4
Objectives	#7	Specific objectives or hypotheses	2-4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	5-5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4-5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7-9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10-11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10-11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10-11
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10-11

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	5
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Efficacy of Autologous Plateletpheresis in Adult Aortic Surgery: Study Protocol for a Randomised Controlled Trial

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Efficacy of Autologous Plateletpheresis in Adult Aortic Surgery: Study Protocol for a Randomised Controlled Trial

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Abstract (250 words)

Introduction Perioperative coagulopathy is common in patients undergoing aortic surgery, increasing the risk of excessive blood loss and subsequent allogeneic transfusion. Blood conservation has become a vital part of cardiovascular surgery, but measures to protect platelets from destruction by cardiopulmonary bypass (CPB) still are lacking. Autologous platelet concentrate (APC) may have potential benefits for intraoperative blood preservation, but its efficacy has not been studied extensively. This study aims to evaluate the efficacy of APC as a blood conservation technique to reduce blood transfusion in adult aortic surgery.

Methods and analysis This is a prospective, single-center, single-blind randomized controlled trial. A total of 344 adult patients undergoing aortic surgery with CPB will be enrolled and randomized to either the APC group or the control group with a 1:1 randomization ratio. Patients in the APC group will receive autologous plateletpheresis

before heparinization, while those in the control group will not. The primary outcome is the perioperative packed red blood cell (pRBC) transfusion rate. Secondary endpoints include the volume of perioperative pRBC transfusion; drainage volume within 72 hours post-surgery; postoperative coagulation and platelet function; and the incidence of adverse events. Data will be analyzed according to the intention-to-treat principle.

Ethics and dissemination This study was approved by the institutional review board of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (**No.2022-1806**). All procedures included in this study will be performed in adherence to the Helsinki Declaration. The results of the trial will be published in an international peer-reviewed journal.

Trial registration number Chinese Clinical Trial Register (ChiCTR2200065834)

Key words plateletpheresis; aortic surgery; transfusion

Strengths and limitations of this study:

1. This is a randomized controlled trial that will enroll eligible adult patients undergoing aortic surgery with CPB, who will be randomly assigned in a 1:1 ratio to either the APC or control group.
2. A total of 344 participants will be recruited for this study to ensure sufficient statistical power.
3. Both quantitative and qualitative data will be collected at multiple time points for subsequent analysis.
4. This trial will be conducted at a single center, which may limit generalizability.
5. In consideration of heterogeneity, this study will exclude high-risk populations such as juveniles, adults over the age of 65, and individuals undergoing thoracoabdominal aorta replacement.

INTRODUCTION

Aortic surgery is associated with increased bleeding. Consumption and dilution of coagulation factors, activation of the systemic inflammatory response and fibrinolysis, ischemia-reperfusion injury, surgical trauma, usage of deep hypothermic circulatory

arrest (HCA), and acquired thrombocytopenia and thrombocytopathy resulted by prolonged cardiopulmonary bypass (CPB) lead to perioperative coagulation disorders, which increases the risk of excessive blood loss and subsequent allogeneic transfusion. Studies have shown that platelet concentrate (PC) transfusion is the first line treatment for assumed hemostatic impairment[1, 2], and in adult patients with active bleeding, a single unit of platelets is expected to increase platelet count by an average of $15\text{-}25\times10^9$ /L[1].

According to the data of Fuwai Hospital in 2013, the annual perioperative PC transfusion rate in cardiovascular surgery was 11.67%. The highest rates of PC transfusion were observed in patients undergoing descending thoracic aorta replacement (100%) and total aortic arch replacement and stented elephant trunk implantation (91.49%). Furthermore, the average PC transfusion volume administered to patients was (1.53±1.20) units, with the largest average volume being administered to patients undergoing thoracic descending aorta replacement was (3.07±1.59) units. However, allogeneic transfusion is associated with an increased rate of postoperative pulmonary complications, infections, transfusion-related circulatory overload, prolonged mechanical ventilation duration, prolonged hospital length of stay, total hospitalization cost, and an increase in in-hospital mortality in patients undergoing aortic surgery[3]. Recent research found that transfusion of packed red blood cells (pRBC), fresh frozen plasma (FFP), or PC is associated with mortality and infection after cardiac surgery in a dose-dependent manner[4]. Therefore, blood conservation has become a vital part of cardiovascular surgery.

The implementation of patient blood management (PBM) in cardiac surgery, which includes correcting preoperative anemia, reducing intraoperative hemodilution, and administering antifibrinolytic drugs, has been demonstrated to be a safe and effective approach to reduce allogeneic blood transfusion, improve clinical outcomes, and conserve blood resources[5-8]. Moreover, autologous pre-donation of blood products, blood salvaging systems, cell saver techniques, minimized pump prime, pharmacologic agents, and autologous reinfusion have been demonstrated to confer advantages. However, measures to protect platelets from destruction by CPB still are

lacking. Autologous platelet-rich plasmapheresis (APP) is a novel method of autologous blood transfusion. In this procedure, whole blood is collected into a citrate-treated bag via the central vein and then centrifuged at a rate of 2,400 to 3,500 rpm in a platelet separation device. This centrifugation separates the whole blood into RBCs, platelet-poor plasma (PPP), and platelet-rich plasma (PRP) based on specific gravity. This technique has been found to effectively protect platelets from damage and has been utilized in cardiovascular surgery[8-11]. A recent clinical trial has demonstrated that the utilization of APP results in a 34% decrease in pRBC transfusion rate, a 52.8% decrease in FFP transfusion rate, and a 56.7% decrease in PC transfusion rate, along with a decrease in hospitalization duration and costs associated with blood transfusion[9]. However, conflicting results have been reported regarding the use of APP in cardiac surgery as it is unclear whether this harvest process is associated with hemodynamic instability, which could potentially lead to organ ischemia[12]. Autologous platelet concentrate (APC) is characterized by a higher platelet count than aPRP, and its harvest process has a minimal impact on hemodynamics. We hypothesized that the use of APC produced through autologous plateletpheresis can reduce perioperative allogeneic blood transfusion in patients undergoing aortic surgery without any impact on perioperative adverse events. To verify our hypothesis, we designed a randomized controlled trial to investigate the efficacy of autologous plateletpheresis in adult aortic surgery.

METHODS AND ANALYSIS

Study design

It is a prospective, single-center, and single-blind randomized controlled trial that will enroll eligible adult patients undergoing aortic surgery with CPB, who have given their informed consent to participate (Supplementary file 1). The patients will be randomly assigned in a 1:1 ratio to either the APC or control group. The APC group will undergo autologous plateletpheresis before heparinization, whereas the control group will not. To ensure the blinding of the study, the intensive care unit (ICU) staff, nurses, outcome assessors, data collectors, and data analysts will not be aware of the patient grouping.

Data will be collected after central venous catheterization (T0), before heparinization (T1), end of surgery (T2), 24 hours post-surgery (T3), 48 hours post-surgery (T4), and 72 hours post-surgery (T5) until discharge. The study protocol is reported following the Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT)[13] and the data will be analyzed according to the intention-to-treat principle. The study flowchart is shown in Figure 1.

Study population

We plan to enroll 344 adult patients who are scheduled to undergo aortic surgery with CPB at Fuwai Hospital in Beijing, China. Eligible participants must meet the following inclusion criteria: (1) diagnosis of aortic disease (including aortic aneurysm, aortic dissection, and aortic coarctation) and scheduled for elective cardiac surgery with CPB, (2) American Society of Anaesthesiologists (ASA) classification I-III, (3) adult patients aged 18-65 years, with a weight of over 50 kg, (4) platelet counts over 150×10^9/L, (5) willingness to provide informed consent for participation in the study.

Patients who present with any of the following exclusion criteria will not be eligible for enrollment: (1) history of platelet donation within 15 days prior to surgery, (2) preoperative cardiogenic shock, cardiac arrest, severe systolic hypotension, oxygen saturation of mixed venose blood (SvO_2) < 75%, on mechanical circulatory support, (3) thrombocytopenia, platelet dysfunction (as diagnosed by thrombelastogram platelet mapping) or any other known history of a bleeding disorder, (4) thromboembolic disease (such as pulmonary embolism, spontaneous arterial thrombosis, or familial hypercoagulability), (5) intellectual or legal disabilities, (6) severe renal impairment (serum creatinine level of >3.3 mg/dL), (7) stroke (history/acute), (8) vitamin K and/or vitamin C deficiency, (9) allergy or contraindication to citrate anticoagulants or its components, (10) breastfeeding or pregnancy, (11) trauma with multiple organ injury, and (12) current enrolment in another perioperative interventional study.

Randomization and blinding

The participants in this study will be divided into two groups, the APC group and the control group, using a computer-generated random number sequence. The participants will be assigned to each group in a 1:1 ratio using simple randomization. The results of the randomization will be kept confidential and stored in envelopes with a 5-digit randomization number written on the cover. The envelopes will be opened in sequential order according to the participant's selected time, to determine the group assignment. To minimize potential bias, the operators and evaluators will be selected from different physician teams. The anesthesiologist will be informed of the participant's group assignment after endotracheal intubation, as the intervention requires their cooperation. The study is designed as a single-blind trial in consideration of the potential subjective bias that could arise from the anesthesiologist's knowledge of the participant grouping, despite the implementation of blinding measures for the surgeon, ICU staff, nurses, outcome evaluators, data collectors, and data analysts.

Anesthesia induction and maintenance

The patients selected for the study received a standardized anesthesia method. Vital signs will be monitored through Electrocardiogram (ECG), oxygen saturation (SpO_2), and invasive blood pressure through the left radial artery/brachial artery and left dorsalis pedis artery/femoral artery when entering the operating room. Baseline measurements of hemodynamic parameters will be obtained by measuring and recording Bispectral index (BIS) and regional cerebral oxygen saturation ($rScO_2$). Induction of intubation will be facilitated with a combination of midazolam (0.05-0.1 mg/kg), etomidate (0.2-0.3 mg/kg), sufentanil (0.5-1 μg/kg), and cisatracurium (0.2 mg/kg). A protective ventilation strategy will be employed, with a tidal volume (VT) of 6-7 ml/kg, Positive end-expiratory pressure (PEEP) of 4-8 mmHg, Fraction of inspiration O_2 (FiO_2) of 0.5-1.0, and ventilation rate adjusted to maintain an end-tidal partial pressure of carbon dioxide ($PETCO_2$) at 35-45 mmHg. Body temperature will be monitored through the nose and rectum. The dosages of propofol, dexmedetomidine, and sevoflurane will be adjusted to maintain a BIS between 40 and 60, with BIS≤10 during deep hypothermic circulatory arrest (DHCA). Intermittent administration of

sufentanil (0.5-1.0 μg/kg) and cisatracurium (50μg/kg) will be performed. After intubation, both groups received an 8.5Fr three-lumen central venous catheter and an 8.5Fr Swan-Ganz catheter through the right internal jugular vein. Blood transfusion is strictly supervised and follows the indication of blood transfusion published by our center[14]. Standardized intraoperative blood conservation techniques, cell-salvage and pump suction will be used in both groups.

Interventions

After induction of general anesthesia, the platelet separation device (Fresenius Kabi, COM.TEC, equipped with disposable separator pipeline consumables of Fresenius C5L) will be connected to the central vein and Swan-Ganz catheter. The process will be initiated by entering the patient's demographic data including gender, height, weight, hematocrit, platelet count and blood collection rate (usually in the range of 50-80 mL/min) via the Menu key on the device. A balanced salt solution (Ringer's lactate solution) or 9% normal saline is used to maintain vascular volume and hemodynamic stability. The collection should be completed before heparinization. The harvested APC will be stored in citrate-treated bags, kept at room temperature and maintained through oscillation for a maximum of 6 hours, then reinfused to the patient after reversal of heparin. The duration of the whole process for each therapeutic dose typically ranged from 25 to 60 minutes.

Endpoints and definitions

The primary endpoint of the study is the rate of pRBC transfusion during the perioperative period. Secondary endpoints include the volume of perioperative pRBC transfusion; drainage volume; and the incidence of adverse events (major bleeding, re-operation, myocardial infarction, stroke, acute kidney injury, pulmonary insufficiency, postoperative infection, and early mortality). Additionally, other study variables will be mechanical ventilation duration; intensive care unit stay; hospital length of stay; postoperative coagulation, platelet function and the direct cost of transfusions.

Perioperative transfusions are defined as all transfusions given intraoperatively

and within 72 hours of the surgery's end time. This included a period of more than 72 hours in cases of delayed closure. Drainage volume is defined as the volume of fluid collected from pericardial and mediastinal drainage tubes within 72 hours after surgery. Major bleeding is defined as bleeding resulting in death, reoperation due to bleeding, intracranial hemorrhage, transfusion of 5 or more units of pRBCs over 48 hours, or pericardial and mediastinal tube drainage exceeding 2000 mL over 24 hours. We will also use the universal definition of perioperative bleeding (UDPB) classification for a more precise definition of perioperative bleeding[15]. Re-operation is defined as excessive chest tube drainage and/or pericardial tamponade requiring re-operation. Myocardial infarction will be diagnosed based on the development of pathological Q waves on two or more adjacent leads on an ECG, changes indicative of ischemia (ST-segment elevation or depression) on an ECG, and/or a change in the serum level of creatine kinase-muscle/brain of more than 75 μg/L. Stroke will be diagnosed based on the presence of a prolonged (72 hours) or permanent neurological deficit (such as paralysis, weakness, or speech difficulty) that is associated with abnormal results on magnetic resonance imaging or computed tomography scans[16]. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network[17]. The change in renal function will be assessed based on the ratio of the peak serum creatinine level to the preoperative serum creatinine level. A patient will be considered to have mild AKI if the highest ratio is between 1.5 and 2.0, moderate AKI if the highest ratio is between 2.0 and 3.0, and severe AKI if the serum creatinine level is ≥4.0 mg/dL, peak ratio is >3.0, or renal replacement therapy is required. Pulmonary insufficiency will be diagnosed based on the presence of prolonged ventilator support of more than 24 hours, the development of acute respiratory distress syndrome, pulmonary edema, pneumonia, or reintubation. Postoperative infection will be diagnosed based on the presence of clinical signs such as fever, radiographic findings such as new infiltration on chest X-rays or computed tomography scans, positive microbiological culture of an endotracheal aspirate ($\geq 10^6$ colony forming units/mL) or bronchoalveolar lavage ($\geq 10^4$ colony forming units/mL), and leukocytosis. Early mortality is defined as all-cause mortality within 30 days of the index procedure[16]. The direct cost of transfusions is

defined as the charge to the hospital by the blood banking service for the blood product transfusions only, and does not include the cost of administering the transfusions.

Sample size estimation

The sample size calculation will be based primarily on the incidence of perioperative pRBC transfusion rate. According to the data from adult aortic surgeries performed at Fuwai Hospital in 2019, a total of 326 cases of aortic surgery were performed, of which 236 cases received pRBC transfusion. According to the results of previous studies[9, 11], to ensure sufficient detection power, it was estimated conservatively that the perioperative pRBC transfusion rate in the APC group could be reduced by 15% compared to the control group, that is, from 72.39% to 57.39%. The sample size was calculated to be 310 patients, considering a significance level of $\alpha = 0.05$, a power of 0.80, and randomization in a 1:1 ratio. Accounting for potential crossovers, protocol violations, and a 10% loss-to-follow-up rate, 344 patients were expected to be enrolled in the clinical trial.

Statistical analysis

The data collected from the study will be analyzed and presented following the Consolidated Standards of Reporting Trials guidelines, following the intention-to-treat principle. Based on sample size calculation and 10% loss to follow-up, 344 patients will be included (assuming a two-tailed 5% type I error rate and 80% power) and randomized to either the APC group or the control group. One's randomization number will be reserved while the procedure is canceled for some special circumstances. The patient will be excluded and an extra random number will be generated to enroll enough patients to the preset sample size if he/she does not undergo surgery until the end of the trial.

Normal distribution of continuous variables will be tested using the Shapiro-Wilks test. To ensure consistency, continuous variables will be presented as mean ± standard deviation if the variables follow a normal distribution, otherwise median and interquartile range (IQR), categorical variables will be presented as numbers and

percentages. Missing data will be managed via multiple imputations. Continuous variables with normal distribution will be compared by Student's t-test between two groups. Continuous variables with skewed distribution will be compared by Mann-Whitney U test. We will compare categorical variables with the $\chi 2$ test or Fisher's exact test. The Spearman rank correlation test will be utilized to assess the correlation between continuous variables. Regression analysis will be performed if the differences in baseline characteristics between the two groups are statistically significant. A logistic regression model will be used to analyze pRBC transfusion exposure and the outcome events. If the outcome event proved to be rare, a Poisson regression model was used. The outcomes will be presented as a percentage with 95% CI. Sensitivity analysis will include a complete case. After half of the study participants have completed the trial, an interim analysis will be conducted to assess efficacy. The study will be terminated (stopped early) if any of the following occurs: i) The study hypothesis cannot be proved after study completion based on the current findings: the conditional power is less than 80% even if the remaining 50% of total sample size is enrolled; ii) The study violates the ethical standards for obvious safety concerns (such as increased risk in adverse events). Subgroup analyses of the primary and secondary outcomes will be performed based on important patient clinical characteristics, results will be expressed as risk differences.

The analysis will be performed by a dedicated data analyst who is masked to the subjects' group allocation. All the tests in the present study are two-tailed and $P<0.05$ is considered statistically significant.

Data management and quality control

In this study, a well-designed case report form will be used to collect baseline characteristics of eligible patients. Two to three individuals will be trained to assist in the collection of baseline characteristics, including demographic data and medical history. Laboratory test results will be obtained from a digital medical record system. Our trial uses a web-based, paperless data submission system (http://www.medresman.org.cn) for data collection and management. Statistical

analysts will only be able to see de-identified data that does not include any sensitive information. All paper documents are kept in a secure filing cabinet at Fuwai Hospital and must be kept for at least 15 years after the study is completed. After this period, any documents must be discarded with the consent of Fuwai Hospital.

All participants in this trial, including surgeons, anesthesiologists, ICU staff, nurses, outcome evaluators, data collectors, and data analysts, will receive uniform training to be familiar with the detailed procedures of the trial before the enrollment of the first patient. The Clinical Trial Steering Committee is composed of the chief supervisor and five members who have over five years of clinical trial experience. The committee is responsible for organizing biweekly meetings to address any trial-related issues and oversee the conduct and progress of the trial. Five commissioners will coordinate the work of relevant departments and provide necessary support to the trial.

Patient and public involvement

In our study, we prioritize the active involvement of patients, anesthesiologists, ICU staff, nurses, and surgeons from the early stages and throughout the study to ensure their comprehension and endorsement of the study results. During the study design phase, we consulted with five hospitalized patients scheduled to undergo aortic surgery. These individuals provided invaluable feedback on recruitment strategies, timing of data collection, and participant communication. This engagement helped to ensure that the study design was centered on the needs of patients. Moreover, involving patients and patient organizations will be essential for disseminating the trial's results to the wider public.

Study status

The trial enrolled its first patient in November 2022 and is scheduled to end in December 2024. As of the time of manuscript submission, 10 participants have been enrolled in the study.

ETHICS AND DISSEMINATION

This study has been approved by the Ethics Committee of Fuwai Hospital (**No.2022-1806**) and has been registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn/), with the registry number ChiCTR2200065834. All procedures included in this study will be performed in adherence to the Helsinki Declaration. The results of the trial will be published in an international peer-reviewed journal.

DISCUSSION

This is currently the first randomized controlled trial to evaluate the efficacy of autologous plateletpheresis in adult patients undergoing aortic surgery. The autologous plateletpheresis method we will perform in this study is a novel approach that has not been previously investigated, which will provide important implications for adult cardiac surgery. We hypothesized that the use of APC produced through autologous plateletpheresis can reduce perioperative allogeneic blood transfusion in patients undergoing aortic surgery without any impact on perioperative adverse events.

Perioperative coagulopathy and bleeding are common complications in cardiovascular surgery with CPB and result in an increased rate of allogeneic blood transfusion. Complex aortic surgery, in particular, is often performed with DHCA, which plays a key role in cerebral protection[18, 19]. Nonetheless, aortic surgery with DHCA is strongly linked with prolonged CPB time, deep hypothermia, and excessive consumption of coagulation factors, which increase the likelihood of requiring allogeneic blood products[20]. Establishing a reasonable PBM program may be an effective strategy for conserving blood resources in these populations.

Cardiac surgery with CPB often is associated with low platelet counts and platelet dysfunction[21, 22]. Platelets have been extensively studied for their crucial functions in maintaining vascular integrity to prevent spontaneous hemorrhage and for primary hemostasis, which involves the cessation of bleeding upon vascular injury[23]. Following injury, platelets interact with various adhesive proteins of the exposed subendothelium through membrane glycoprotein (GP) receptors, including integrins, immunoglobulin-like receptors and the leucine-rich repeats of the GPIb-V-IX complex,

resulting in platelet adhesion. This adhesion allows for the interaction of GPVI with collagen, which initiates platelet activation and the release of δ -granule contents, such as adenosine diphosphate, adenosine triphosphate and serotonin, and the synthesis of thromboxane A2[23]. These soluble secondary agonists, together with thrombin generated at the site of injury, contribute to further platelet activation, resulting in the binding of soluble fibrinogen to the activated α IIb β 3 integrin and the formation of a platelet-fibrin plug that seals the breach and stops bleeding[24]. Platelet transfusion is therefore the primary therapy for patients with thrombocytopenia or platelet dysfunction who require procedures or surgery.

Although allogeneic platelet transfusion can effectively improve coagulation function, it may not be an adequate solution to this problem due to the risks associated with massive allogeneic blood transfusion. Autologous blood transfusion was long considered safer on the ground of immunization and viral risks, as it reduces the exposure to various donors[24, 25]. In 1977, Harke and colleagues[26] first reported the use of APP in cardiac surgery. Then in 1987, Ferrari et al[27] performed perioperative plasmapheresis to collect aPRP and demonstrated a reduction in blood loss and the need for allogeneic blood transfusion. Since then, APP has been widely used in cardiovascular surgery because it sets aside a subset of the patient's own platelets from the circulation during surgery and prevents exposure of that platelet subset to the CPB circuit, decreasing the risk of global platelet dysfunction[8, 9, 28]. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recommended in 2011[29] indicating that APP may be a reasonable approach to support blood conservation strategies in high-risk patients if an adequate yield can be reliably obtained (Class IIa, Level of Evidence A). However, the results of these studies are not consistent. Van et al[30] demonstrated that APP can reduce neither perioperative blood transfusions nor blood loss. Triulzi et al[31] found that APP reduced postoperative blood loss, but there was no significant reduction in perioperative allogeneic blood transfusions, so they did not support the use of APP in low-risk cardiac surgery. Since then, the use of APP has declined gradually, as their effectiveness and applicability have been controversial. The volume of blood collected for obtaining sufficient

platelets is around 20-30% of the total blood volume, potentially resulting in circulatory instability and aggravate hemodilution due to fluid overload.

In comparison to the traditional APP process, the autologous plateletpheresis method implemented in this trial did not require the extraction of a large volume of whole blood, but rather utilized an external circulation to sustain a stabilized quantity of isolated blood of approximately 170 ml, thereby avoiding excessive hemodilution and circulatory instability. The efficacy of PC transfusions in hemostasis depends on the achievement of both platelet count and clot quality[2, 32, 33]. Current study[34] demonstrates that the APC procedure does not result in platelet dysfunction. Furthermore, APC usually contains 3-4 $\times 10^{11}$ platelets in approximately 300 ml of plasma, which is significantly higher than PC. Transfusion of one APC unit will raise the platelet count by approximately 30×10^3cells/μl[35], which seems to be a more effective hemostatic approach in cardiovascular surgery. Moreover, the patient selection process will be based on widely accepted platelet donation criteria. Patients with preoperative platelet counts ranging from 150-450*10^9 /L will be included, as a low platelet count before surgery may increase the risk of intraoperative hemorrhage, while a high platelet count may indicate an underlying disease or a higher risk of thrombosis[36]. Hence, this study ensures a high level of safety.

LIMITATIONS

Our trial has certain limitations that need to be acknowledged. Firstly, this will be a single-center trial so the result may not be generalizable to all centers due to some inevitable confusion, thus a multi-center study with a large sample size will be needed in the future. Secondly, research has shown that females have a higher rate of pRBC transfusions than males due to lower RBC counts, Hb levels, and circulating blood volume. As this study includes a wide range of patients, there may be differences in baseline characteristics, such as gender, and multivariate correction will be utilized in statistical analysis to mitigate potential bias[37-40]. Additionally, patients undergoing aortic surgery in our center tend to have more complex diseases, leading to increased postoperative transfusion requirements compared to other centers. Therefore, this study

will exclude high-risk populations, including juveniles, adults over the age of 65, and individuals undergoing thoracoabdominal aorta replacement, to account for heterogeneity.

Contributors JG and HJ conceived the study and initiated the study design. JJ, XG and HJ will be involved in study implementation. JG provided statistical expertise in clinical trial design and will conduct the statistical analysis. GJ, JJ, XG and HJ will provide expertise with data interpretation. All authors participated, read and approved the final manuscript.

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Data statement The final trial data for this protocol could be supplied on reasonable request.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1. Flowchart of the study. The flowchart depicts the participant timeline and trial design, commencing from participant enrollment and subsequent allocation to either the APC group or control group, and concluding with perioperative management of both groups. APC, Autologous platelet concentrate.

Supplementary file 1. Model consent form of the study.

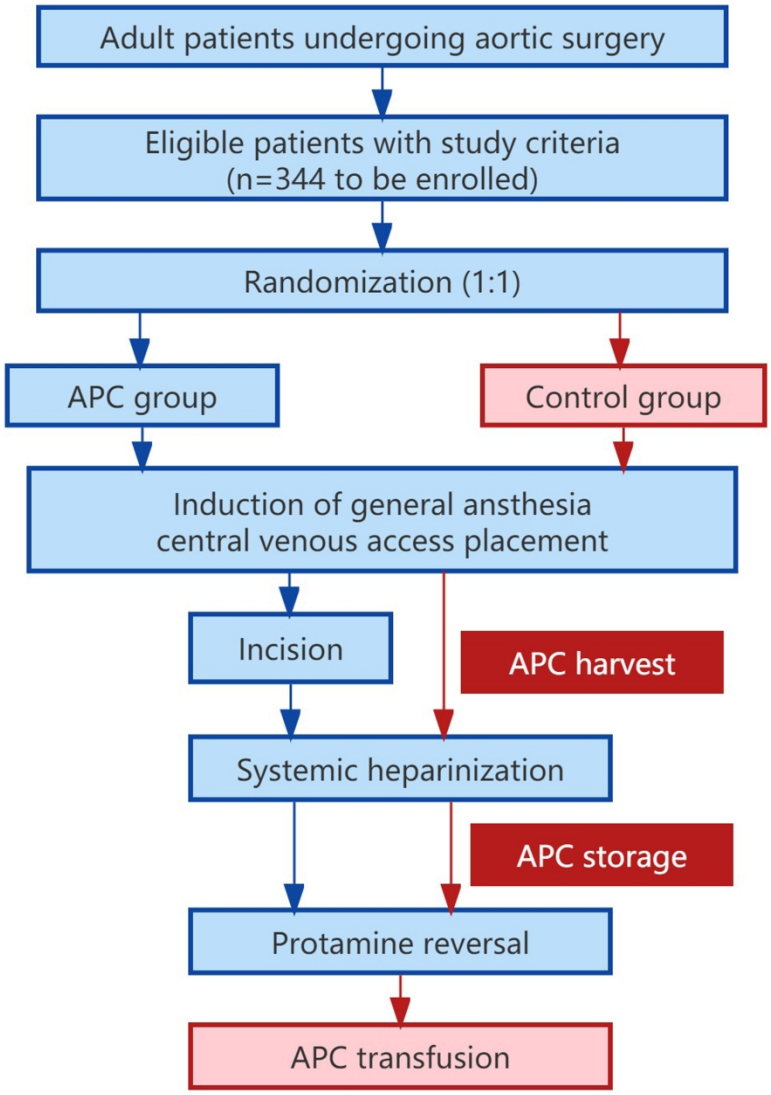

Figure 1. Flowchart of the study. The flowchart depicts the participant timeline and trial design, commencing from participant enrollment and subsequent allocation to either the APC group or control group, and concluding with perioperative management of both groups. APC, Autologous platelet concentrate.

385x526mm (300 x 300 DPI)

知情同意书

我们邀请您参加由中国医学科学院阜外医院发起、中国医学科学院输血研究所资助的“主动脉手术患者体外循环前血小板单采的有效性研究”。本研究已通过中国医学科学院阜外医院伦理委员会审批(电话 010-88396281)。请仔细阅读说明，了解您在研究中的权利和义务，明确研究性质和风险。参加研究属完全自愿，无论是否参加本研究都不会影响您在医院期间的治疗。当研究人员向您说明和讨论知情同意书时，您可以随时提问并让研究人员向您解释您不明白的地方。您可以与家人、朋友以及您的医生讨论之后再做决定。

若您目前正参加其他临床研究，请告知研究人员。

本项研究的项目负责人是纪宏文教授（中国医学科学院阜外医院输血科），本项研究的资助方是中国医学科学院输血研究所。本研究为单中心研究。

一、为什么进行这项研究？

在您即将进行的手术中，可能对血小板的功能及数量造成损伤。血小板数量减少、功能损伤是体外循环心血管手术后大量出血的最主要原因。为保证您的生命安全，麻醉医师或外科医师可能给您输注其他人的血液成分。但目前血源紧张的现状可能会导致异体血液供应不及时。除此之外，大量输注异体血液成分也可能会带来感染、输血相关性肺损伤和免疫反应等重大安全问题。最大限度减少异体血液成分的输入是世界医学发展的趋势，更是降低您发生相关风险的措施。

同时，由于主动脉手术异体血小板的输注率较高，如果不能及时得到血小板将会延误手术进程，增加您的手术风险。单采自体血小板的使用，将节约了等待异体血小板的时间，且血小板采自您本身，不存在异体血制品所带来的免疫原性和传染性风险。

二、为什么邀您请参加这项研究？

根据您目前的疾病初步诊断和检查结果，医生可能会建议您进行体外循环下主动脉手术，所以我们邀请您参加本项研究。是否最终入选由研究医生根据您的实际情况来判断。临床医生根据以下入选条件决定您能否最终参加试验：

入选标准（以下全部符合才能入组试验）：

1、在中国医学科学院阜外医院接受体外循环下主动脉手术，且术前申请异体血小板；

2、年龄 18～65 周岁，体重 50 公斤以上；

3、抗血小板药物停药时间>5 天，或明确血小板功能正常；

4、采前血小板计数：≥150×10^9 / L；

5、需同时满足施行心脏外科手术标准及麻醉标准，并签署知情同意书。

排除标准（符合以下任何一条，则不能入组本试验）：

1、合并其他心肺脑疾病、感染、临床明确诊断的严重的肝肾功能不全、临床明确诊断的凝血功能异常，或出于任何原因不能配合研究，例如语言理解，精神疾病等；

2、15 天内有血小板采集史；

3、术前出现心源性休克、心脏骤停、严重低血压；

4、拒绝输血；

5、参与其他药物器械临床试验未完成者；

6、研究者认为不宜纳入本试验的其他原因。

三、多少人将参与这项研究？

本研究为前瞻性单中心临床研究，计划在本中心入组共 344 名患者。

四、参加本项研究，需要您做什么？

您自愿参加并签署经伦理委员会批准的知情同意书后，即进入研究程序，并需要按照以下流程配合研究各阶段相关工作。

1、筛选期

在您入选研究前，医生将询问、记录您的病史，并采集您常规诊疗过程中的实验室检查检验数据。如果您是育龄期妇女，还请您完成妊娠试验，以确定您是否可以参加该临床研究。请您知悉，这些检查均为您手术前需要进行的常规检查，不会因为您参加本研究而额外增加：

1）实验室检查：血常规；血生化；凝血功能；血栓弹力图（如有）；细胞因子（如有）；

2）心电图、超声心动图；

3）CT 平扫（如有）；CT 血管成像；

4）必要时妊娠检查。

2、手术期

如果医生判断您符合本研究的入选条件，您可自愿参加研究，签署知情同意书。如您不愿参加研究，我们将按照常规方法治疗，即围术期根据输血指征，在必要时输入异体血液成分。

若您自愿参加研究，将按以下步骤进入研究：

您将被随机分到两组：A 组（单采组）：麻醉后体外循环前，采集自体血小板保存，体外循环结束中和肝素后，A 组先将预先采集的血小板回输给受试者本人，随后根据输血指征输入异体血液成分。C 组（对照组）：不进行自体血小板采集，在体外循环结束中和肝素后

根据输血指征输入异体血液成分。单组与对照组的样本量比例为 1：1。

医生将收集手术期间与您相关的数据和资料包括手术期间生命体征，用药情况，手术时间，体外循环时间，围手术期其他血液保护措施，术中输液和输血的资料，术中失血量等。

3、随访期

您需要在手术后出院前完成随访及实验室检查，包括：血常规检查，血栓弹力图检查，凝血功能检查等。同时，医生将收集与您相关的数据和资料包括：术后引流量，术后输异体血成分/量，住院时间和住院费用等。

五、本项研究会持续多久？

本研究计划持续时间为 2022 年 11 月至 2024 年 12 月，您预计参与本研究的持续时间为自您手术前签署知情同意书开始，至您出院时为止。

六、参加本研究受试者可能的风险？

研究过程中您处于全身麻醉状态，不会产生疼痛或刺激，研究全程在严密的生命体征监护下由经验丰富的麻醉医师、外科医师和护士的严密观察下进行，保证您的安全。可能发生的主要不良反应及治疗措施如下：

（1）感染：预防性使用抗生素；

（2）低血钙：医生会根据血钙水平变化及临床表现给予相应治疗。轻度无需处理，较严重时给予静脉注射钙剂对症治疗；

（3）低血压：轻度无需处理；较严重时给予缩血管药物对症治疗。

七、参加本研究受试者可能的受益？

本研究采用的血小板分离技术与无偿献血者捐献血小板时采用的技术相同，具有良好的安全性。本实施方式遵循《中华人民共和国国家卫生健康委员会 2022 版围手术期患者血液管理指南》中推荐的围术期血液保护方法；本研究采用的血小板分离技术与无偿献血者捐献血小板时采用的技术相同，具有良好的安全性。

您可能因参与本研究减少输注异体血液成分，从而减少与输血相关的不良反应的发生，如输血相关的感染、输血反应、输血相关肺损伤、输血相关免疫抑制等，同时降低输血相关费用，减轻您的经济负担。

此外，您的参与将为患者血液管理质量改善干预措施提供新的思路及数据支持，也为国家未来制定有关行业政策提供参考和依据，具有社会意义。

八、如果不参加此研究，有没有其他备选治疗方案？

您可以选择不参加本项研究，这对您获得常规治疗不会带来任何不良影响。

目前针对您拟施行的手术方式，阜外医院常规的输血治疗方法即为术前常规提交输血小板申请，待备血流程完成后安排手术；围术期根据您的实验室检查结果（血常规，血气分析，血栓弹力图等），若符合输血指征，即输入异体血液成分，此部分费用需要您自己承担。

九、参加该项研究的费用和补偿

无论您是否参加本研究，您的检验检查费用、手术费用及日常随访护理费用将没有什么不同。您参加研究过程中，各阶段的费用和补偿情况如下：

1、筛选期

研究医生将根据您入院后、手术前的各项检查检验结果（同上述）判定您是否符合本研究纳入标准，并签署知情同意书。您的这些检查检验结果将被采集作为基线评估。在签署知情同意书后，您不需要额外进行其他检查。上述检查为手术前需进行的常规检查，无论您是否参与本研究都要进行，由您自身承担。

2、手术期

若您符合本研究入选条件，申办者将免费为您提供手术过程中研究相关的检验费用，包括：血常规检查，血栓弹力图检查，凝血功能检查，细胞因子检测。

本研究在采集自体血小板过程中，需要使用专用的血细胞分离一次性耗材、储血袋和技术服务费用，属于医保 A 类报销项目，由您自身承担，具体收费标准如下：根据受试者术前血小板计数检查结果，可采集 1～2 个治疗量血小板，每次采集收费 1900 元，采集费用需要受试者承担。（目前输注异体血小板每 1 个治疗量收费 1500 元，与采集 1 个治疗量自体血小板的费用相当，如果采集 2 个自体血小板可节约 1100 元费用。）

3、随访期

您需要在手术后出院前完成随访及实验室检查，包括：血常规检查，血栓弹力图检查，凝血功能检查，细胞因子检测。上述检查为手术患者术后常规检查项目，不因是否参加本研究而产生变化，因此费用由您自身承担。

本研究无受试者补贴。

十、发生研究相关损害的处理？

本研究所采用的核心技术与血站无偿献血技术相同，具有充分的安全性依据。如果您在试验过程中有任何不适，可随时与研究者联系，他/她会给予您相应的指导。如因参加研究导致您受到损害，您有权及时获得免费治疗，并有权按照国家相关法律法规获得赔偿或补偿。

十一、我的信息会得到保密吗？

是的，您的信息在研究中将严格保密。本试验中使用您的研究数据时，您的个人信息都

是保密的，您的所有信息资料将得到妥善保存并仅供研究使用。

研究数据库中的信息会严格脱敏消除个人身份识别特征，可能识别您身份的信息将不会透露给研究人员以外任何人，除非获得您的许可。

在不违反保密原则和相关法规的情况下，申办方、伦理委员会和药品监督管理部门、卫生健康主管部门的检查人员可以查阅受试者的原始医学记录，以核实临床试验的过程和数据。

如果研究结果公开发表，您个人信息不会出现在任何公开病历资料和出版物中，我们也不会向任何人、任何机构透露此信息。

十二、与研究相关的新信息？

在试验过程中我们可能会获知有关治疗的新的信息，我们会及时通知您，让您决定是否继续参加研究或退出。

十三、是否一定要参加并完成本项研究？

是否参加本项研究是自愿的，您可以自由决定参加或拒绝参加此项研究。无论您是否同意参与此项研究，均不会影响您在我院就诊期间所应享有的临床常规诊疗措施。

本临床试验遵循《赫尔辛基宣言》有关人体试验的相关规定，并获得阜外医院医学伦理委员会批准，这将会保证您的权益在本试验中不受侵犯。如果您想参加此项研究，您需要认真阅读本知情同意书，确认充分了解相关问题后签署本知情同意书。您不会因为签署本文件而失去法律赋予您的任何合法权利。

您阅读此须知后若有疑问，请尽量询问。如果您同意签署本文件，中国医学科学院阜外医院将无偿获得您的生物样本和研究数据，本院研究者和参与本研究的共同研究机构可出于本研究目的使用您的生物样本和研究数据。

您可以在在任何时间拒绝参加或有权在研究期间的任何阶段随时退出研究，而不需要任何理由，也不会受到歧视或者报复，相应的医疗待遇与权益均不受影响。

如果您参加过程中想退出研究项目，请通知研究人员，按研究人员要求完成退出前相关检查，并根据要求以书面形式完成有关退出手续；退出后研究人员将不再继续收集并使用您的试验数据，但在您退出前已匿名化采集的数据将无法删除或撤回。退出后，您可以选择常规输血方式，若您退出后，发现新的与您健康和权益相关的信息时，我们可能会再次与您联系。

十四、如果有问题或困难，该与谁联系？

您可以在任何时间提出有关本项试验的任何问题，并得到相应的解答，包括临床试验期间可能出现的任何不适，请联系研究医生 纪宏文 ，联系电话 010-88322881 。

如果您对自己的权益有任何疑问，请联系中国医学科学院阜外医院伦理委员会，电话：010-88396281。

感谢您花时间阅读本知情同意书。如果您及您的家属通过充分考虑之后同意参加本临床试验，希望您及您的家属能按照研究人员的要求完成本次临床试验。参加本试验前，请与您的研究人员共同完成并签署此文件最后一页（签署页），一式两份，您和医院各保留一份签署的文件。

十五、致谢

医学科学的发展和进步离不开临床试验，您的参与将为医学科学的进步做出奉献。作为此项研究的申办者及研究者，我们将时刻铭记您的奉献，并对您表示最诚挚的感谢！

签署页

我已经认真阅读、理解并同意本知情同意书全部条款。

我已被告知此项研究的目的、内容、程序，研究可能的风险，以及我的权益等；我有足够的时间和机会进行提问，并得到了令我满意答复。

我同意参加本研究并授权你院采集我的血液标本及研究数据用于本研究。

我承诺我提供的信息是真实的；如提供了虚假信息，我承诺对其后果负责。

我确认签名处所留联系方式为我本人有效联系方式，如变更联系方式应及时告知你院，否则，我愿意承担无法联系及无法收到通知的相应后果。

我知道我可以随时退出此项试验，并不影响我应该得到的医疗待遇与权益。

我将得到这份知情同意书的正本一份，上面包含我和研究者的签名。

我同意参加本项研究。

受试者姓名（楷体）：_____ 签名：_____

联系电话：_____ 日期：_____

（如受试者为无行为能力人或限制行为能力人时，需监护人签署）

监护人姓名：_____ 签名：_____

与患者关系：_____ 联系电话：_____

我确认，在知情同意书中的信息是被正确解释了的并且受试者和/或受试者合法代表明白理解了这些信息。受试者自愿同意参加本研究。

研究者：_____ 签名：_____

日期：_____

公正见证人【如适用】：_____ 日期：_____

联系人：_____ 联系电话：_____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-4
Objectives	#7	Specific objectives or hypotheses	2-4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4-12
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	4-5

		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 and figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9

Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a	10-11

		description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10-11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these	9-10

		interim results and make the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10-11
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2, 12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4-5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10-11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10-11
Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	n/a

trial care		and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 12, 15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 1
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a