

BMJ Open Efficacy of autologous plateletpheresis in adult aortic surgery: study protocol for a randomised controlled trial

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ABSTRACT

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) are still 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-centre, single-blind randomised controlled trial. A total of 344 adult patients undergoing aortic surgery with CPB will be enrolled and randomised to either the APC group or the control group with a 1:1 randomisation ratio. Patients in the APC group will receive autologous plateletpheresis before heparinisation, 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 analysed 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).

INTRODUCTION

Aortic surgery is associated with increased bleeding. Consumption and dilution of coagulation factors, activation of the systemic inflammatory response and fibrinolysis, ischaemia-reperfusion injury, surgical trauma, usage of deep hypothermic circulatory arrest, and acquired thrombocytopenia and thrombocytopenia resulted by prolonged cardiopulmonary bypass (CPB) lead to perioperative coagulation disorders, which increase the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a randomised controlled trial that will enrol eligible adult patients undergoing aortic surgery with cardiopulmonary bypass, who will be randomly assigned in a 1:1 ratio to either the autologous platelet concentrate or control group.
- ⇒ A total of 344 participants will be recruited for this study to ensure sufficient statistical power.
- ⇒ Both quantitative and qualitative data will be collected at multiple time points for subsequent analysis.
- ⇒ This trial will be conducted at a single centre, which may limit generalisability.
- ⇒ In consideration of heterogeneity, this study will exclude high-risk populations such as juveniles, adults over the age of 65 years and individuals undergoing thoracoabdominal aorta replacement.

risk of excessive blood loss and subsequent allogeneic transfusion. Studies have shown that platelet concentrate (PC) transfusion is the first-line treatment for assumed haemostatic 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 $15\text{--}25 \times 10^9/\text{L}$.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 hospitalisation cost and an increase in in-hospital

mortality in patients undergoing aortic surgery.³ Recent research found that transfusion of packed red blood cells (pRBCs), 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 anaemia, reducing intraoperative haemodilution 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, minimised pump prime, pharmacological agents and autologous reinfusion have been demonstrated to confer advantages. However, measures to protect platelets from destruction by CPB are still 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 2400–3500 rpm in a platelet-separation device. This centrifugation separates the whole blood into RBCs, platelet-poor plasma and platelet-rich plasma (PRP) based on specific gravity. This technique has been found to effectively protect platelets from damage and has been used in cardiovascular surgery.^{8–11} A recent clinical trial has demonstrated that the utilisation 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 hospitalisation 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 haemodynamic instability, which could potentially lead to organ ischaemia.¹² Autologous platelet concentrate (APC) is characterised by a higher platelet count than autologous PRP (aPRP), and its harvest process has a minimal impact on haemodynamics. We hypothesised 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 randomised controlled trial to investigate the efficacy of autologous plateletpheresis in adult aortic surgery.

METHODS AND ANALYSIS

Study design

It is a prospective, single-centre and single-blind randomised controlled trial that will enrol eligible adult patients undergoing aortic surgery with CPB, who have given their informed consent to participate (online supplemental file 1). The patients will be randomly assigned in a 1:1 ratio to either the APC or control group.

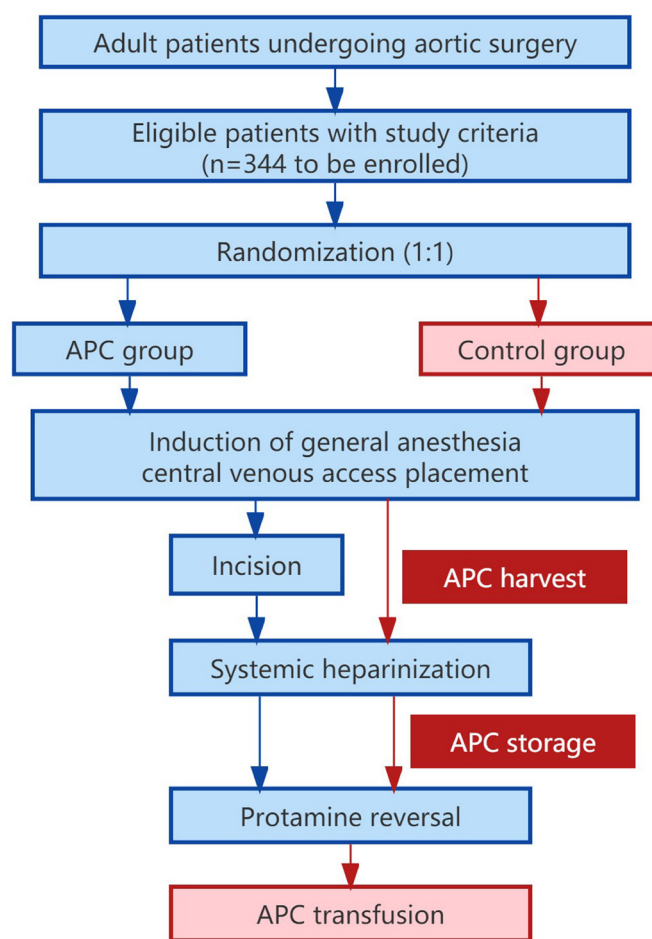


Figure 1 Flow chart of the study. The flow chart depicts the participant timeline and trial design, commencing from participant enrolment and subsequent allocation to either the APC group or control group, and concluding with perioperative management of both groups. APC, autologous platelet concentrate.

The APC group will undergo autologous plateletpheresis before heparinisation, 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 catheterisation (T0), before heparinisation (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 2013,¹³ and the data will be analysed according to the intention-to-treat principle. The study flow chart is shown in figure 1.

Study population

We plan to enrol 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 Anesthesiologists classification I–III; (3) adult patients aged 18–65 years, with a weight of over 50 kg; (4) platelet counts over $150 \times 10^9/L$; (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 enrolment: (1) history of platelet donation within 15 days prior to surgery; (2) preoperative cardiogenic shock, cardiac arrest, severe systolic hypotension, oxygen saturation of mixed venous blood $<75\%$, 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 $>3.3 \text{ mg/dL}$); (7) stroke (history/acute); (8) vitamin K and/or vitamin C deficiency; (9) allergy or contraindication to citrate anticoagulants or its components; (10) breast feeding or pregnancy; (11) trauma with multiple organ injury and (12) current enrolment in another perioperative interventional study.

Randomisation 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 randomisation. The results of the randomisation will be kept confidential and stored in envelopes with a 5-digit randomisation 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 minimise potential bias, the operators and evaluators will be selected from different physician teams. The anaesthesiologist 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 anaesthesiologist'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.

Anaesthesia induction and maintenance

The patients selected for the study received a standardised anaesthesia method. Vital signs will be monitored through ECG, oxygen saturation, 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 haemodynamic parameters will be obtained by measuring and recording bispectral index (BIS) and regional cerebral oxygen saturation. Induction of intubation will be

facilitated with a combination of midazolam ($0.05\text{--}0.1 \text{ mg/kg}$), etomidate ($0.2\text{--}0.3 \text{ mg/kg}$), sufentanil ($0.5\text{--}1 \mu\text{g/kg}$) and cisatracurium (0.2 mg/kg). A protective ventilation strategy will be employed, with a tidal volume of $6\text{--}7 \text{ mL/kg}$, positive end-expiratory pressure of $4\text{--}8 \text{ mm Hg}$, fractional inspired oxygen of $0.5\text{--}1.0$ and ventilation rate adjusted to maintain an end-tidal partial pressure of carbon dioxide at $35\text{--}45 \text{ mm Hg}$. 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 $\text{BIS} \leq 10$ during deep hypothermic circulatory arrest (DHCA). Intermittent administration of sufentanil ($0.5\text{--}1.0 \mu\text{g/kg}$) and cisatracurium ($50 \mu\text{g/kg}$) will be performed. After intubation, both groups received an 8.5 Fr three-lumen central venous catheter and an 8.5 Fr Swan-Ganz catheter through the right internal jugular vein. Blood transfusion is strictly supervised and follows the indication of blood transfusion published by our centre.¹⁴ Standardised intraoperative blood conservation techniques, cell salvage and pump suction will be used in both groups.

Interventions

After induction of general anaesthesia, 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, haematocrit, platelet count and blood collection rate (usually in the range of $50\text{--}80 \text{ mL/min}$) 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 haemodynamic stability. The collection should be completed before heparinisation. 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 min.

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, reoperation, myocardial infarction, stroke, acute kidney injury, pulmonary insufficiency, postoperative infection and early mortality). Additionally, other study variables will be mechanical ventilation duration; ICU 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 haemorrhage, transfusion of five 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 classification for a more precise definition of perioperative bleeding.¹⁵ Reoperation is defined as excessive chest tube drainage and/or pericardial tamponade requiring reoperation. 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 ischaemia (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 MRI or CT 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 oedema, 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 CT 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 leucocytosis. 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 with 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 randomisation 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 analysed 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 randomised to either the APC group or the control group. One's randomisation number will be reserved while the procedure is cancelled for some special circumstances. The patient will be excluded and an extra random number will be generated to enrol 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-Wilk test. To ensure consistency, continuous variables will be presented as mean \pm SD if the variables follow a normal distribution, otherwise median and 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 χ^2 test or Fisher's exact test. The Spearman rank correlation test will be used 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 analyse 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: (1) the study hypothesis cannot be proven 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; (2) 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 do 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, anaesthesiologists, 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 enrolment of the first patient. The Clinical Trial Steering Committee is composed of the chief supervisor and five members who have over 5 years of clinical trial experience. The committee is responsible for organising 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 prioritise the active involvement of patients, anaesthesiologists, 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 hospitalised 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 centred on the needs of patients. Moreover, involving patients and patient organisations 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 randomised 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 hypothesised 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 programme may be an effective strategy for conserving blood resources in these populations.

Cardiac surgery with CPB is often 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 haemorrhage and for primary haemostasis, 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 GPIIb-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 ADP, ATP 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 immunisation and viral risks, as it reduces the exposure to various donors.^{24 25} In 1977, Harke *et al*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 2011²⁹ 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 der Wal *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 aggravates haemodilution due to fluid overload.

In comparison with 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 used an external circulation to sustain a stabilised quantity of isolated blood of approximately 170 mL, thereby avoiding excessive haemodilution and circulatory instability. The efficacy of PC transfusions in haemostasis depends on the achievement of both platelet count and clot quality.^{2 32 33} Current study³⁴ demonstrates that the APC procedure does not result in platelet dysfunction. Furthermore, APC usually contains more than 1000×10^9 /L platelets in approximately 300 mL of plasma, which is significantly higher than PC.³⁵ Transfusion of one APC unit will raise the platelet count by approximately 30×10^3 cells/ μ L,³⁵ which seems to be a more effective haemostatic 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 to 450×10^9 /L will be included, as a low platelet count before surgery may increase the risk of intraoperative haemorrhage, 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. First, this will be a single-centre trial so the result may not be generalisable to all centres due to some inevitable confusion; thus, a multicentre study with a large sample size will be needed in the future. Second, research

has shown that females have a higher rate of pRBC transfusions than males due to lower RBC counts, haemoglobin 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 used in statistical analysis to mitigate potential bias.^{37–40} Additionally, patients undergoing aortic surgery in our centre tend to have more complex diseases, leading to increased postoperative transfusion requirements compared with other centres. Therefore, this study will exclude high-risk populations, including juveniles, adults over the age of 65 years and individuals undergoing thoracoabdominal aorta replacement, to account for heterogeneity.

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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. JG, JJ, XG and HJ will provide expertise in data interpretation. All authors participated, read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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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: *****)。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、为什么邀请您参加这项研究?

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: $\geq 150 \times 10^9 / L$;

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知情同意书-主动脉手术患者体外循环前血小板单采的有效性研究 V1.1 2022-08-25 2 / 7

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,您的个人信息都知情同意书-主动脉手术患者体外循环前血小板单采的有效性研究

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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研究？

是否参加本研究是自愿的，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 *****，联系电话 *****。

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：

*****。

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。

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