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 alloimmune 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 346 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 International Peer-reviewed Journal.

Trial registration number Chinese Clinical Trial Register (ChiCTR200065834).

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 resulting by prolonged cardiopulmonary bypass (CPB) lead to perioperative coagulation disorders, which increase the risk of excessive blood loss and subsequent alloimmune transfusion. Studies have shown that platelet concentrate (PC) transfusion is the first-line treatment for assumed haemostatic impairment, and in adult patients with active bleeding, a single unit of platelets is expected to increase platelet count by an average of 15–25×10^9/L.

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 3.07±1.59 units. However, alloimmune 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 platelethpheresis 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 platelethpheresis 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.

The APC group will undergo autologous platelethpheresis 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,\textsuperscript{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 × 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 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 (0.05–0.1 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 of 6–7 mL/kg, positive end-expiratory pressure of 4–8 cm Hg, fractional inspired oxygen of 0.5–1.0 and ventilation rate adjusted to maintain an end-tidal partial pressure of carbon dioxide at 35–45 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 BIS ≤10 during deep hypothermic circulatory arrest (DHCA). Intermittent administration of sufentanil (0.5–1.0 µg/kg) and cisatracurium (50 µg/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. 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 50–80 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 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. 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. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network.16 Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network.16 Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network. Acute kidney injury (AKI) will be diagnosed following the criteria of the Acute Kidney Injury Network. 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 (≥ 10^6 colony-forming units/mL) or bronchoalveolar lavage (≥ 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, 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 α=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±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 χ2 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 analysis 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 platelepheresis in adult patients undergoing aortic surgery. The autologous platelepheresis 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 platelepheresis 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. 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. 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. 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. 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 ADP, ATP and serotonin, and the synthesis of thromboxane A2. 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. 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. In 1977, Harke et al. first reported...
the use of APP in cardiac surgery. Then in 1987, Ferrari et al. 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. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recommended in 2011 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. demonstrated that APP can reduce neither perioperative blood transfusions nor blood loss. Triulzi et al. 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. Current study demonstrates that the APC procedure does not result in platelet dysfunction. Furthermore, APC usually contains more than 1000×10⁹/L 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 30×10⁹cells/µL, 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 450×10⁹/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.

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 multivariable correction will be used in statistical analysis to mitigate potential bias.

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. 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.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplemental material

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