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Prospective study of preoperative autologous blood donation for patient with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial

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Abstract

Introduction

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery. Better blood management to avoid anemia and reduce allogeneic blood transfusion after spine surgery become increasingly important with development of the concept of enhanced recovery after surgery (ERAS). We present here the design of a randomized controlled trial with three groups to verify the clinical effectiveness of PABD in patients at high risk of transfusion for lumbar fusion surgery and explore the optimal timing of autologous blood donation.

Method and analysis

Patients (age 18-70 years) who will receive lumbar fusion surgery for degenerative disease with hemoglobin over 110g/L and "high risk" of allogeneic blood transfusion are eligible, unless they refuse participation or are diagnosed with malignant metastases, infection, cardiovascular and cerebrovascular diseases, and critical illnesses. A total of 1200 patients will be recruited and randomized into three groups. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Primary outcome

measures will include hemoglobin decline, incidence and amount of allogeneic blood transfusion. Secondary outcome measures will include days of hospitalization after surgery, incidence of complications and nerve function recovery. This study is a single-centre and open-label randomized controlled trial. The sample size is calculated with reference to the retrospective data and previous studies.

Ethics and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02). Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

Trial registration number: ChiCTR2000039824, pre-results.

Strengths and limitations of this study

- This is a randomized controlled trial based on retrospective study with large sample size in recent years at the same centre.
- A validated risk score system will be implemented in the patient recruitment to ensure the necessity and validity of this trial.
- Participants and treating surgeons are not blinded to the intervention under evaluation.

INTRODUCTION

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery [1, 2]. Allogeneic blood transfusion is safe in our opinion currently but usually limited in clinical practice due to increasing blood shortage[3], and there are still inherent risks for allogeneic blood transfusion[4-6]. Autologous blood transfusion techniques involve the collection and reinfusion of the patient's own blood with PABD being the common used form[7-9].

Elective surgery in Orthopedics like spine or hip procedures is often associated with massive blood loss and high risk of anemia after surgery[6, 10, 11]. Delayed wound healing and infection could be related to anemia after surgery, and those are more susceptible and severe in orthopedics due to the implant. Additionally, anemia contributes to higher cardiac burden and may affect the functional exercise in the early postoperative period, which is essential for patients who underwent orthopedic surgery. With the development of the concept of enhanced recovery after surgery (ERAS) in recent years, better blood management to avoid anemia after surgery becomes increasingly important. In addition to an alternative in allogeneic blood shortage[12], there are also other advantages about PABD. It can be used for patients with rare blood groups, multiple allo-antibodies or religious objections to allogeneic transfusion[13]. However, we should also be careful about this technique especially for the necessity, indication, and cost-effectiveness in the clinical practice[14]. PABD program should be a multidisciplinary issue and based on a discussion between doctor and patient

regarding the procedure's risks and benefits.

Surgical procedures with high risk of allogeneic blood transfusion should be considered for PABD[9]. The less likely the transfusion, the more likely donated blood will not be used. Lumbar fusion surgery for patients with degenerative lumbar spine diseases often results in massive blood loss due to long time of operation, large wound and high difficulty to stop bleeding in the spinal canal area. All levels of anemia were reported to be significantly associated with prolonged length of hospitalization and poorer operative or 30-days outcomes in patients undergoing elective spine surgery.[15] Blood management could be essential especially for patients with spine deformity and long segments fusion. Kennedy et al. found that PABD was more efficient in patients who underwent instrumentation fusion but not all spine surgery[16]. Solves et al. also reported that PABD significantly decreased the allogeneic blood transfusion for spine instrumentation fusion in young patients[17]. However, it is still controversial about the appliance and effectiveness of PABD in spine surgery. Brookfield et al. reported that it is not beneficial for patients who underwent short lumbar spine fusion with normal blood coagulation[18]. Cohort study by Kelly et al. revealed that there is no protective effect of PABD against the risk of allogeneic blood transfusion for adult patients who underwent spine deformity surgery[19]. Moreover, evidence about the timing of blood donation in PABD program still remains insufficient[14, 20]. More evidence about the appliance and effectiveness of PABD in spine surgery is warranted. In this randomized clinical trial, we aim to verify the clinical effectiveness of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery with respect to the incidence and number of allogeneic blood transfusion, hemoglobin (Hgb) decline, days of hospitalization after surgery, complications and nerve function recovery. Study design of different time interval between blood donation and surgery help us to explore the optimal timing of autologous blood donation simultaneously.

METHOD

Study design

This study is planned to be a prospective and open-label randomized controlled trial with three groups. (**Figure 1**)

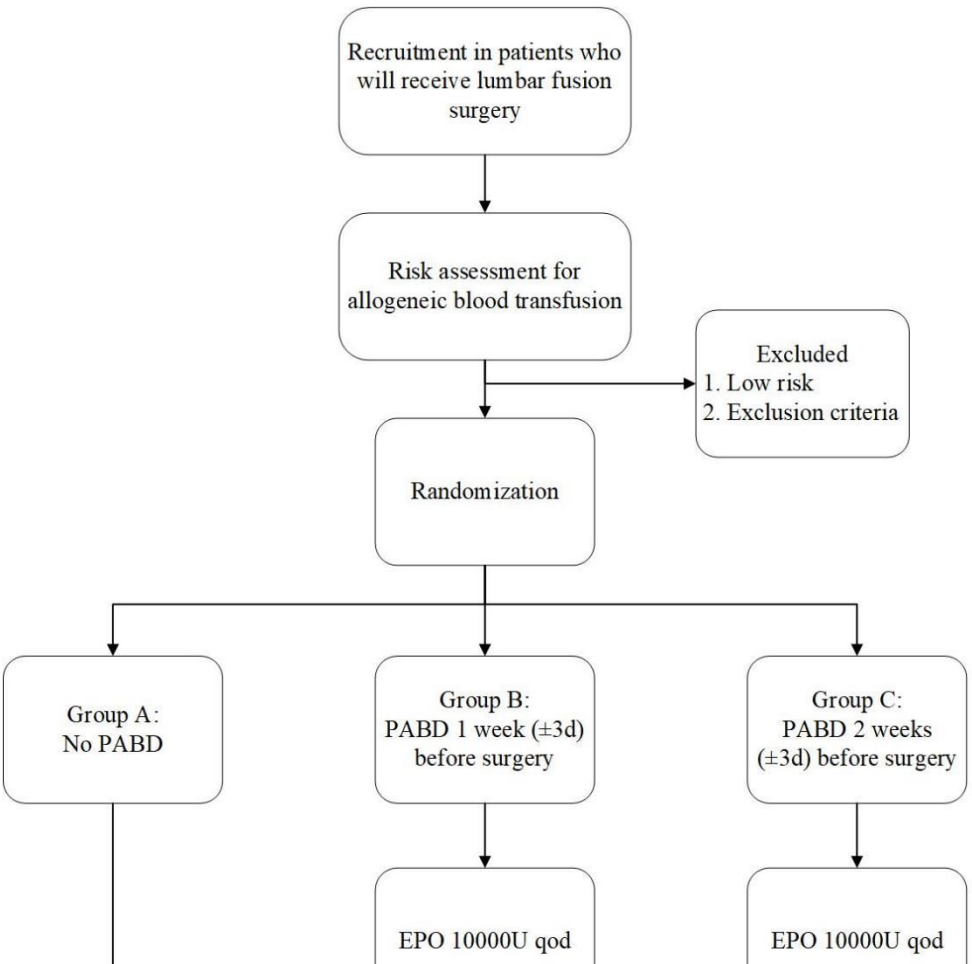

Figure 1 Study design

Recruitment and informed consent

This single-centre study will be conducted in the Peking University Third Hospital (PUTH). Eligible participants will be recruited from the patients who are going to receive lumbar fusion surgery in a three-years period by our researchers. Recruitment, assessment and randomization will be finished in the Inpatient Management Centre (IMC) that is in charge of pre-operative evaluation before patients' admission. Researchers will discuss with eligible patients when they have decided to receive lumbar fusion surgery and then finish the informed consent. After enrolment, participants will be coded as a unique number and general information will be recorded.

Eligibility

Inclusion criteria

a. Patients who will receive elective lumbar fusion surgery for lumbar degenerative disease
b. Age between 18 and 70 years
c. Hgb over 110 g/L
d. "High risk" for the risk score of allogeneic blood transfusion for lumbar fusion surgery

Exclusion criteria

a. Diagnosed with malignant metastases
b. Infectious diseases
c. Cardiovascular and cerebrovascular diseases such as coronary heart disease and severe aortic stenosis
d. Critically ill patients
e. Refuse to participate for any reason

Randomization

Participants recruited from the IMC in PUTH will be randomized to three groups via random number method. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Randomization of the three groups will be on a 1:1:1 basis.

Blinding

Participants and surgeons will not be blinded to the interventions. As the PABD plans should be informed to patients clearly. The assessment after surgery will be performed by research assistants who are blinded to the recruitment and randomization. Allogeneic blood transfusion triggers will be still up to the discretion of surgeons. Researchers will not participate in the decision of allogeneic blood transfusion.

Interventions

Blood donation and transfusion

All eligible participants will be randomized to three groups after pre-operative evaluation. Participants in group A will not receive PABD and regarded as control group. Donation of 400ml autologous blood will be finished once at 1 week (±3d) before surgery for participants in group B and 2 weeks (±3d) before surgery for group C. We also allow participants to finish the donation 3 days before or after the time points in consideration of the feasibility in practice. All donated blood in our study will be transfused back during operation. Autologous blood donation, cryopreservation and transfusion during surgery will be assisted and finished by department of Blood Transfusion and Anesthesiology. Patients in group B and C will be given subcutaneous injection of 10000U erythropoietin (EPO) qod until the date of surgery.

Table 1 Time schedule of interventions

Interventions	Admission	1-2 weeks before surgery	Intraoperation
Pre-operative evaluation	√		
Blood donation		√	
EPO injection		√	
Autologous blood transfusion			√

EPO, erythropoietin.

Assessment and management

We have established a risk score of allogeneic blood transfusion for lumbar fusion surgery in the preliminary study. This score system consist of six parameters including age, BMI index, number of fusion and fixation segments, spine deformity and Hgb level (**Table 2**). The risk score of allogeneic blood transfusion for lumbar fusion surgery was established based on the retrospective data of 5101 cases of lumbar spine surgery in the past two years from 2018 to 2019. We have performed preliminary validation for the risk score system in the patients from January to June 2020 prospectively. The effectiveness was acceptable with sensitivity of 76% (AUC=0.83).

All participants will be assessed at outpatient and IMC, including demographic information, height and weight, blood test and radiographic examination. Spine surgeons will make a general surgical plan including fusion and fixation segments. Patients with low risk of allogeneic blood transfusion will be excluded from our study. Assessments and follow-up will be maintained at one day before surgery, one day before discharge, and one month after surgery **(Table 3)**.

Table 2 Risk score of allogeneic blood transfusion for lumbar fusion surgery

Characteristic	Score
Age	
<60 years	0
≥60 years	1
BMI	

≥18.5	0
<18.5	1
No. of fusion segments	
1	1
2	2
3	3
≥4	4
No. of fixation segments	
2	1
3	2
4	3
≥5	4
Spine deformity	
No	0
Yes	1
Hemoglobin (g/L)	
≥140	0
125-140	1
<125	2

BMI, body mass index. Total score 0-4 = low risk; Total score 5-13 = high risk.

Table 3 Time schedule of assessments

Assessments	1 day before surgery	1 day before discharge	1 month after surgery
Hgb	√	√	
VAS	√	√	√
ODI	√		√
SF-36	√		√
Complications		√	√

Hgb, hemoglobin; VAS, visual analogue score; ODI, oswestry disability index.

Outcome measurements

Primary outcome

Incidence of allogeneic blood transfusion

Intraoperative or postoperative allogeneic blood transfusion will be recorded as binary outcome. Incidence of allogeneic blood transfusion will be statistically compared as primary outcome.

Amount of allogeneic blood transfusion

Total number(ml) of allogeneic blood transfusion for each patient in three groups will be recorded as continuous outcome and analysed as the primary outcome.

Hgb decline

Hgb decline(g/L) from one day before surgery to one day before discharge will be recorded as continuous outcome and analysed as one of the primary outcomes.

Secondary outcome

Days of hospitalization after surgery

Length of hospitalization after surgery could be an indicator for recovery and will be recorded as continuous outcome in this study. Days of hospitalization will be compared and statistically analysed as secondary outcome.

Incidence of complications

Wound infection and hematoma until 1 month after surgery will be recorded as associated complications. Complications will be recorded as binary outcome and regarded as secondary outcome.

Nerve function improvement

Oswestry disability index (ODI) is a typical tool for the evaluation of disability in lumbar spine surgery[21]. The improvement rate of ODI after surgery from one day before surgery to one month after surgery will be recorded as continuous outcome and analysed as secondary outcome.

Data management

Each patient will receive a unique number and all data will be recorded with this number. An attending spine surgeon and a research assistant will be in charge of the examination and assessment in the perioperative period. Research assistant will maintain the follow-up one month after surgery. Data entry and transfer will be performed by two staff and two computers. All data including baseline information, risk score, Hgb result, allogeneic blood transfusion and ability assessments will be secured in PUTH and the access will be restricted to the research team. Database will be established after finishing all the data collection and back-ups will be made in multiple disks. All raw data will be kept in the Medical record department.

Patient and public involvement

Patients or public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Safety monitoring and adverse events

Participants in this study will receive PABD before lumbar spine surgery. All participants will be observed for 40 minutes after blood donation. Patients with Hgb less than 110g/L, infectious diseases, cardiovascular or cerebrovascular diseases will be excluded from our study in consideration of safety. Strictly standard collection and storage processes will be performed and monitored by department of IMC and Blood Transfusion. All expected or unexpected adverse events from this study will be

recorded and monitored. Patients suffered from any adverse events related to the interventions in research will receive free treatment.

Sample size calculation

There were 5101 cases of lumbar fusion surgery from Jan 2018 to Nov 2019 and 817 cases received allogeneic blood transfusion. The incidence of allogeneic blood transfusion was 16%. The preliminary study of PABD from Aug 2020 to Sep 2020 demonstrated that the incidence of allogeneic blood transfusion decreased 18% compared with the same time period in 2019. We hypothesize that the incidence of allogeneic blood transfusion decreased by 18% via PABD for patients at "high risk" score for lumbar fusion surgery. We should recruit 400 patients for both group PABD and non-PABD. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate and accuracy rate of 80% for risk score system. On the other hand, a single injection of EPO was reported to result in Hgb increase of 2.9g/L in adolescence[22]. We hypothesize that a single injection of EPO could attain Hgb increase of 2.5 g/L in adults who are going to receive lumbar fusion surgery, the Hgb level in group C before surgery should be 10 g/L more than patients in group B and we assume to be 120g/L and 110g/L, respectively. Then we should recruit 330 patients for both group B and C. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate. To sum up, we will recruit a total of 1200 patients for three groups.

Statistical analysis

The baseline characteristics of all participants will be summarized by group and presented as means (SD) for continuous variables, and count (%) for categorial variables. Incidence of allogeneic blood transfusion and complications will be measured as binary outcome. Amount of allogeneic blood transfusion (ml), Hgb decline, days of hospitalization after surgery and improvement rate of ODI will be measured as continuous outcome. Chi-square test and logistical regression will be used for the binary outcome. Nonparametric test or t test will be performed for continuous outcome according to the distribution. A value of $P<0.05$ will be considered as statistically significant. All analysis will be performed using SPSS 17.0 by a researcher who is blinded to recruitment and data collection.

Ethic and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02) and registered on Chictr.org (registration number: ChiCTR2000039824). Informed consent will be obtained for all participants. Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

DISCUSSION

We have presented the rationale and design of a prospective randomized controlled trial to compare the outcomes of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery. The RCT will compare the outcome among three

groups to verify the clinical effectiveness of PABD and explore the optimal timing of blood donation with adjuvant EPO injection in lumbar fusion surgery.

In the previous studies of PABD, the time interval between first blood donation and surgery varied from less than 2 weeks to more than 4 weeks[14, 20]. Adequate time interval was thought to be crucial for the red blood cell (RBC) regeneration of donated blood[23]. But it should also be noted that there is an outdate for the donated blood in plastic bags. An appropriate time interval to balance the regeneration and preservation of donated blood is significant for the efficiency of PABD program. We choose an interval of 1 to 2 weeks to reduce the storage time of donated blood in autologous blood bank. Meanwhile, adjuvant EPO injection after blood donation will be used for all patients in group B and C to accelerate the RBC regeneration. EPO injection was reported to be useful for increasing the RBC before hip surgery and avoiding allogeneic transfusion during spinal deformity surgery in PABD program[22, 24]. To explore the optimal timing of autologous blood donation with EPO injection is also one of the main goals in this prospective study.

In this study, a validated risk score system of allogeneic blood transfusion for lumbar fusion surgery based on retrospective study with large sample size will be implemented to ensure the necessity for PABD program. Both this technique and EPO injection should be more efficient in the patients with higher risk of blood transfusion[20, 25]. Waste of donated blood was an inherent risk for PABD program[26, 27]. The review by Singbartl et. al reported that the wastage of unneeded PABD units varied from 18% to above 50%[28]. All donated blood in our study will be storage for a relatively shorter time period and transfused back during operation. This design aims to eliminate the waste of donated blood and simultaneously decrease the risk of allogeneic blood transfusion in peri-operative period for targeted patients who will receive lumbar fusion surgery. A multidisciplinary cooperation including department of IMC, Blood Transfusion, Anesthesiology and Orthopedics in the hospital will ensure the safety and feasibility of this prospective trial in clinical practice.

Contributors NX and YZ contributed to design the trial and drafted the manuscript. YT contributed to design the trial and oversaw the manuscript writing and submission. NX, YZ, YT, BL, HQ, XZ, NY, WL (Wei Li), CZ, WL (Weishi Li) and WF contributed to the trial design and have read and approved this manuscript.

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Competing interests None declared.

Patient consent No identifiable patient pictures or data have been involved in the protocol.

Ethics approval This trial has been approved by Peking University Third Hospital

Medical Science Research Ethic Committee (No: 2020-262-02).

Provenance and peer review Not commissioned; externally peer reviewed.

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For "Prospective study of preoperative autologous blood donation for patient with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial"

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (√)
Funding	4	Sources and types of financial, material, and other support (P10)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P10)
	5b	Name and contact information for the trial sponsor (P10)
	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 (P10)
	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)
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 (P2-P3)
	6b	Explanation for choice of comparators (P3, P7-P8)
Objectives	7	Specific objectives or hypotheses (P3)

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, noninferiority, exploratory) (P3-P4)
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 (P5)
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) (P5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P5-P7)
	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) (P8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P5-P8)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P8)
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 (P7-P8)
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) (P6-P7)
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 (P9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P5)
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 (P5)
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 (P5 & P8)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P5 & P8)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P5)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P5)
Methods: Data collection, management, and analysis		
Data collection methods	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 (P5-P8)
	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
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 (P8)
Statistical methods	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 (P9)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P9)
	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) (P9)

Methods: Monitoring

Data monitoring	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 (P8)
	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
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 (P8)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P9)
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) (P9)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P10)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P8)
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 (P8)

Dissemination policy	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 (P8)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P8)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prospective study of preoperative autologous blood donation for patients with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial

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Prospective study of preoperative autologous blood donation for patients with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial

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Abstract

Introduction

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery. Better blood management to avoid anemia and reduce allogeneic blood transfusion after spine surgery become increasingly important with development of enhanced recovery after surgery (ERAS). We present here the design of a randomized controlled trial with three groups to verify the clinical effectiveness of PABD in patients at high risk of transfusion for lumbar fusion surgery and explore the optimal timing of autologous blood donation.

Method and analysis

Patients (age 18-70 years) who will receive lumbar fusion surgery for degenerative disease with hemoglobin over 110g/L and "high risk" of allogeneic blood transfusion are eligible, unless they refuse participation or are diagnosed with malignant metastases, infection, cardiovascular and cerebrovascular diseases, hematological disorders or relevant drug history, and critical illnesses. A total of 1200 patients will be recruited and randomized into three groups. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Primary outcome measures will include hemoglobin

decline, incidence and amount of allogeneic blood transfusion. Secondary outcome measures will include days of hospitalization after surgery, hematocrit level and incidence of complications. This study is a single-centre and open-label randomized controlled trial. The sample size is calculated with reference to the retrospective data and previous studies.

Ethics and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02). Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

Trial registration number: ChiCTR2000039824, pre-results.

Strengths and limitations of this study

- This is a randomized controlled trial based on retrospective study with large sample size in recent years at the same centre.
- A validated risk score system will be implemented in the patient recruitment to ensure the necessity and validity of this trial.
- Participants and treating surgeons are not blinded to the intervention under evaluation.

INTRODUCTION

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery [1, 2]. Allogeneic blood transfusion is safe in our opinion currently but usually limited in clinical practice due to increasing blood shortage[3], and there are still inherent risks for allogeneic blood transfusion[4-6]. Autologous blood transfusion techniques involve the collection and reinfusion of the patient's own blood with PABD being the common used form[7-9].

Elective surgery in Orthopedics like spine or hip procedures is often associated with massive blood loss and high risk of anemia after surgery[6, 10, 11]. Delayed wound healing and infection could be related to anemia after surgery, and those are more susceptible and severe in orthopedics due to the implant. Additionally, anemia contributes to higher cardiac burden and may affect the functional exercise in the early postoperative period, which is essential for patients who underwent orthopedic surgery. With the development of the concept of enhanced recovery after surgery (ERAS) in recent years, better blood management to avoid anemia after surgery becomes increasingly important. In addition to an alternative in allogeneic blood shortage[12], there are also other advantages about PABD. It can be used for patients with rare blood groups, multiple allo-antibodies or religious objections to allogeneic transfusion[13]. However, we should also be careful about this technique especially for the necessity, indication, and cost-effectiveness in the clinical practice[14]. PABD program should be a multidisciplinary issue and based on a discussion between doctor and patient

regarding the procedure's risks and benefits.

Surgical procedures with high risk of allogeneic blood transfusion should be considered for PABD[9]. The less likely the transfusion, the more likely donated blood will not be used. Lumbar fusion surgery for patients with degenerative lumbar spine diseases often results in massive blood loss due to long time of operation, large wound and high difficulty to stop bleeding in the spinal canal area. All levels of anemia were reported to be significantly associated with prolonged length of hospitalization and poorer operative or 30-days outcomes in patients undergoing elective spine surgery.[15] Blood management could be essential especially for patients with spine deformity and long segments fusion. Kennedy et al. found that PABD was more efficient in patients who underwent instrumentation fusion but not all spine surgery[16]. Solves et al. also reported that PABD significantly decreased the allogeneic blood transfusion for spine instrumentation fusion in young patients[17]. However, it is still controversial about the appliance and effectiveness of PABD in spine surgery. Brookfield et al. reported that it is not beneficial for patients who underwent short lumbar spine fusion with normal blood coagulation[18]. Cohort study by Kelly et al. revealed that there is no protective effect of PABD against the risk of allogeneic blood transfusion for adult patients who underwent spine deformity surgery[19]. Moreover, evidence about the timing of blood donation in PABD program still remains insufficient[14, 20]. More evidence about the appliance and effectiveness of PABD in spine surgery is warranted. In this randomized clinical trial, we aim to verify the clinical effectiveness of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery with respect to the incidence and number of allogeneic blood transfusion, hemoglobin (Hgb) decline, days of hospitalization after surgery, hematocrit level and incidence of complications. Study design of different time interval between blood donation and surgery help us to explore the optimal timing of autologous blood donation simultaneously.

METHOD

Study design

This study is planned to be a prospective and open-label randomized controlled trial with three groups. (**Figure 1**)

Recruitment and informed consent

This single-centre study will be conducted in the Peking University Third Hospital (PUTH). Eligible participants will be recruited from the patients who are going to receive lumbar fusion surgery in a three-years period by our researchers. Recruitment, assessment and randomization will be finished in the Inpatient Management Centre (IMC) that is in charge of pre-operative evaluation before patients' admission. Researchers will discuss with eligible patients when they have decided to receive lumbar fusion surgery and then finish the informed consent. After enrolment, participants will be coded as a unique number and general information will be recorded.

Eligibility

Inclusion criteria

a. Patients who will receive elective lumbar fusion surgery for lumbar degenerative disease
b. Age between 18 and 70 years
c. Hgb over 110 g/L
d. "High risk" for the risk score of allogeneic blood transfusion for lumbar fusion surgery

Exclusion criteria

a. Diagnosed with malignant metastases
b. Infectious diseases
c. Cardiovascular and cerebrovascular diseases such as coronary heart disease and severe aortic stenosis
d. Hematological disorders or drug history which are not suitable for blood donation
e. Critically ill patients
f. Refuse to participate for any reason

Randomization

Eligible participants recruited from the IMC in PUTH will be randomized to three groups via random number method by researcher who is blinded for outcome collection. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Randomization of the three groups will be on a 1:1:1 basis.

Blinding

Participants and surgeons will not be blinded to the interventions. As the PABD plans should be informed to patients clearly. The assessment after surgery will be performed by research assistants who are blinded to the recruitment and randomization.

Interventions

Blood donation and transfusion

All eligible participants will be randomized to three groups after pre-operative evaluation. Participants in group A will not receive PABD and regarded as control group. Donation of 400ml autologous blood will be finished once at 1 week (±3d) before surgery for participants in group B and 2 weeks (±3d) before surgery for group C. We also allow participants to finish the donation 3 days before or after the time points in consideration of the feasibility in practice. All donated blood in our study will be transfused back during surgery unless the haemoglobin level is still above 125 g/L for male and 115 g/L for female before wound closure, then the autologous blood will not be transfused and be storage until the discharge of patients. Tranexamic acid and intraoperative blood salvage will be applied in three groups as usual. Autologous blood donation, preservation at 2 to 6 degree centigrade in dedicated refrigerator and transfusion during surgery will be assisted and finished by department of Blood

Transfusion and Anesthesiology. Patients in group B and C will be given subcutaneous injection of 10000U erythropoietin (EPO) every other day (qod) until the date of surgery. Time schedule of interventions can be followed in the **Table 1**.

Table 1 Time schedule of interventions

Interventions	Admission	1-2 weeks before surgery	Peri-operation
Pre-operative evaluation	√		
Blood donation		√	
EPO injection		√	
Autologous blood transfusion			√

EPO, erythropoietin.

Assessment and management

We have established a risk score of allogeneic blood transfusion for lumbar fusion surgery in the preliminary study. This score system consist of six parameters including age, BMI index, number of fusion and fixation segments, spine deformity and Hgb level (**Table 2**). The risk score of allogeneic blood transfusion for lumbar fusion surgery was established based on the retrospective data of 5101 cases of lumbar spine surgery in the past two years from 2018 to 2019. We have performed preliminary validation for the risk score system in the patients from January to June 2020 prospectively. The effectiveness was acceptable with sensitivity of 76% (AUC=0.83).

All participants will be assessed at outpatient and IMC, including demographic information, height and weight, blood test and radiographic examination. Spine surgeons will make a general surgical plan including fusion and fixation segments. Patients with low risk of allogeneic blood transfusion will be excluded from our study. Baseline iron metabolism and vitamin will be screened for all participants. Oral iron supplements and vitamin drugs will be initialed and continued until the day before surgery for patients with iron and vitamin deficiencies. All patients will receive one unit of allogenic blood transfusion if their haemoglobin level drop below 8.0 g/dL and the patient display clinical symptom of anemia (tachycardia and/or hypotension) despite intravenous fluid boluses.

Table 2 Risk score of allogeneic blood transfusion for lumbar fusion surgery

Characteristic	Score
Age	
<60 years	0
≥60 years	1
BMI	
≥18.5	0
<18.5	1
No. of fusion segments	
1	1

2	2
3	3
≥4	4
No. of fixation segments	
2	1
3	2
4	3
≥5	4
Spine deformity	
No	0
Yes	1
Hemoglobin (g/L)	
≥140	0
125-140	1
<125	2

BMI, body mass index. Total score 0-4 = low risk; Total score 5-13 = high risk.

Outcome measurements

Primary outcome

Incidence of allogeneic blood transfusion

Intraoperative or postoperative allogeneic blood transfusion will be recorded as binary outcome. Incidence of allogeneic blood transfusion will be statistically compared as primary outcome.

Amount of allogeneic blood transfusion

Total number(ml) of allogeneic blood transfusion for each patient in three groups will be recorded as continuous outcome and analysed as the primary outcome.

Hgb decline

Hgb decline(g/L) from one day before surgery to one day before discharge will be recorded as continuous outcome and analysed as one of the primary outcomes.

Secondary outcome

Days of hospitalization after surgery

Length of hospitalization after surgery could be an indicator for recovery and will be recorded as continuous outcome in this study. Days of hospitalization after surgery will be compared and statistically analysed as secondary outcome.

Hematocrit level

Hematocrit check will be scheduled weekly for patients in group B and C. Pre-operative hematocrit level will be assessed in group A regularly. Initial and pre-operative

hematocrit level will be compared between two groups receiving EPO administration and recorded as secondary outcome.

Incidence of complications

Wound infection and complications associated with blood transfusion will be recorded as binary outcome and analyzed as secondary outcome

Data management

Each patient will receive a unique number and all data will be recorded with this number. An attending spine surgeon and a research assistant will be in charge of the examination and assessment in the perioperative period. Research assistant will maintain the follow-up one month after surgery. Data entry and transfer will be performed by two staff and two computers. All data including baseline information, risk score, Hgb result, allogeneic blood transfusion and ability assessments will be secured in PUTH and the access will be restricted to the research team. Database will be established after finishing all the data collection and back-ups will be made in multiple disks. All raw data will be kept in the Medical record department.

Patient and public involvement

Patients or public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Safety monitoring and adverse events

Participants in this study will receive PABD before lumbar spine surgery. All participants will be observed for 40 minutes after blood donation. Patients with Hgb less than 110g/L, infectious diseases, cardiovascular or cerebrovascular diseases will be excluded from our study in consideration of safety. Strictly standard collection and storage processes will be performed and monitored by department of IMC and Blood Transfusion. All expected or unexpected adverse events from this study will be recorded and monitored. Patients suffered from any adverse events related to the interventions in research will receive free treatment.

Sample size calculation

There were 5101 cases of lumbar fusion surgery from Jan 2018 to Nov 2019 and 817 cases received allogeneic blood transfusion. The incidence of allogeneic blood transfusion was 16%. The preliminary study of PABD from Aug 2020 to Sep 2020 demonstrated that the incidence of allogeneic blood transfusion decreased by 18% compared with the same time period in 2019. We hypothesize that the incidence of allogeneic blood transfusion decreased by 18% via PABD for patients at “high risk” score for lumbar fusion surgery. We should recruit 400 patients for both group PABD and non-PABD. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate and accuracy rate of 80% for risk score system. On the other hand, a single injection of EPO was reported to result in Hgb increase of 2.9g/L in adolescence[21]. We hypothesize that a single injection of EPO could attain Hgb increase of 2.5 g/L in adults who are going to receive lumbar fusion surgery, the Hgb

level in group C before surgery should be 10 g/L more than patients in group B and we assume to be 120g/L and 110g/L, respectively. Then we should recruit 330 patients for both group B and C. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate. To sum up, we will recruit a total of 1200 patients for three groups.

Statistical analysis

The baseline characteristics of all participants will be summarized by group and presented as means (SD) for continuous variables, and count (%) for categorial variables. All the confounding variables which may influence the primary outcome will be recorded and compared among three groups. Incidence of allogeneic blood transfusion and complications will be measured as binary outcome. Amount of allogeneic blood transfusion (ml), Hgb decline, days of hospitalization after surgery and hematocrit level will be measured as continuous outcome. Chi-square test and logistical regression will be used for the binary outcome. Nonparametric test or t test will be performed for continuous outcome according to the distribution. A value of $P<0.05$ will be considered as statistically significant. All analysis will be performed using SPSS 17.0 by a researcher who is blinded to recruitment and data collection.

Ethic and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02) and registered on Chictr.org (registration number: ChiCTR2000039824). Informed consent will be obtained for all participants. Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

DISCUSSION

We have presented the rationale and design of a prospective randomized controlled trial to compare the outcomes of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery. The RCT will compare the outcome among three groups to verify the clinical effectiveness of PABD and explore the optimal timing of blood donation with adjuvant EPO injection in lumbar fusion surgery.

In the previous studies of PABD, the time interval between first blood donation and surgery varied from less than 2 weeks to more than 4 weeks[14, 20]. Adequate time interval was thought to be crucial for the red blood cell (RBC) regeneration of donated blood[22]. But it should also be noted that there is an outdate for the donated blood in plastic bags. An appropriate time interval to balance the regeneration and preservation of donated blood is significant for the efficiency of PABD program. We choose an interval of 1 to 2 weeks to reduce the storage time of donated blood in autologous blood bank. Meanwhile, adjuvant EPO injection after blood donation will be used for all patients in group B and C to accelerate the RBC regeneration. EPO injection was reported to be useful for increasing the RBC before hip surgery and avoiding allogeneic transfusion during spinal deformity surgery in PABD program[21, 23]. To explore the optimal timing of autologous blood donation with EPO injection is also one of the main goals in this prospective study.

In this study, a validated risk score system of allogeneic blood transfusion for lumbar fusion surgery based on retrospective study with large sample size will be implemented to ensure the necessity for PABD program. Both this technique and EPO injection should be more efficient in the patients with higher risk of blood transfusion[20, 24]. Waste of donated blood was an inherent risk for PABD program[25, 26]. The review by Singbartl et. al reported that the wastage of unneeded PABD units varied from 18% to above 50%[27]. All donated blood in our study will be storage for a relatively shorter time period and transfused back during operation unless the haemoglobin level is still above 125 g/L for male and 115 g/L for female before wound closure, then the autologous blood will not be transfused and be storage until the discharge of patients. This design aims to eliminate the waste of donated blood and simultaneously decrease the risk of allogeneic blood transfusion in peri-operative period for targeted patients who will receive lumbar fusion surgery. A multidisciplinary cooperation including department of IMC, Blood Transfusion, Anesthesiology and Orthopedics in the hospital will ensure the safety and feasibility of this prospective trial in clinical practice.

Contributors NX and YZ contributed to design the trial and drafted the manuscript. YT contributed to design the trial and oversaw the manuscript writing and submission. NX, YZ, YT, BL, HQ, XZ, NY, WL (Wei Li), CZ, WL (Weishi Li) and WF contributed to the trial design and have read and approved this manuscript.

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Competing interests None declared.

Patient consent No identifiable patient pictures or data have been involved in the protocol.

Ethics approval This trial has been approved by Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02).

Provenance and peer review Not commissioned; externally peer reviewed.

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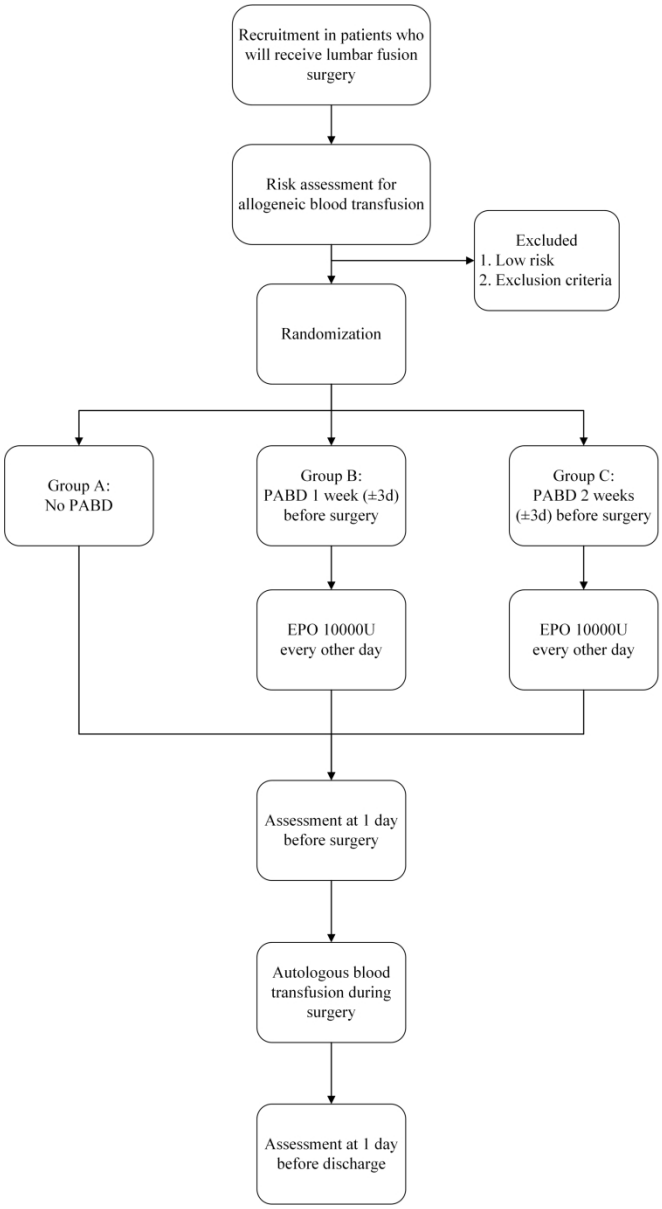

Figure 1 Study design

196x359mm (300 x 300 DPI)

For "Prospective study of preoperative autologous blood donation for patient with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial"

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (√)
Funding	4	Sources and types of financial, material, and other support (P10)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P10)
	5b	Name and contact information for the trial sponsor (P10)
	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 (P10)
	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)
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 (P2-P3)
	6b	Explanation for choice of comparators (P3, P7-P8)
Objectives	7	Specific objectives or hypotheses (P3)

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, noninferiority, exploratory) (P3-P4)
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 (P5)
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) (P5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P5-P7)
	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) (P8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P5-P8)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P8)
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 (P7-P8)
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) (P6-P7)
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 (P9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P5)
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 (P5)
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 (P5 & P8)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P5 & P8)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P5)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P5)
Methods: Data collection, management, and analysis		
Data collection methods	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 (P5-P8)
	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
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 (P8)
Statistical methods	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 (P9)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P9)
	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) (P9)

Methods: Monitoring

Data monitoring	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 (P8)
	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
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 (P8)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P9)
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) (P9)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P10)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P8)
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 (P8)

Dissemination policy	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 (P8)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P8)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prospective study of preoperative autologous blood donation for patients with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial

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Prospective study of preoperative autologous blood donation for patients with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial

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Abstract

Introduction

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery. Better blood management to avoid anemia and reduce allogeneic blood transfusion after spine surgery become increasingly important with development of enhanced recovery after surgery (ERAS). We present here the design of a randomized controlled trial with three groups to verify the clinical effectiveness of PABD in patients at high risk of transfusion for lumbar fusion surgery and explore the optimal timing of autologous blood donation.

Method and analysis

Patients (age 18-70 years) who will receive lumbar fusion surgery for degenerative disease with hemoglobin over 110g/L and "high risk" of allogeneic blood transfusion are eligible, unless they refuse participation or are diagnosed with malignant metastases, infection, cardiovascular and cerebrovascular diseases, hematological disorders or

relevant drug history, and critical illnesses. A total of 1200 patients will be recruited and randomized into three groups. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Primary outcome measures will include hemoglobin decline, incidence and amount of allogeneic blood transfusion. Secondary outcome measures will include days of hospitalization after surgery, hematocrit level and incidence of complications. This study is a single-centre and open-label randomized controlled trial. The sample size is calculated with reference to the retrospective data and previous studies.

Ethics and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02). Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

Trial registration number: ChiCTR2000039824, pre-results.

Strengths and limitations of this study

- This is a randomized controlled trial based on retrospective study with large sample size in recent years at the same centre.
- A validated risk score system will be implemented in the patient recruitment to ensure the necessity and validity of this trial.
- Participants and treating surgeons are not blinded to the intervention under evaluation.

INTRODUCTION

Pre-operative autologous blood donation (PABD) can be used to reduce the exposure of allogeneic blood transfusion in patients undergoing elective surgery [1, 2]. Allogeneic blood transfusion is safe in our opinion currently but usually limited in clinical practice due to increasing blood shortage[3], and there are still inherent risks for allogeneic blood transfusion[4-6]. Autologous blood transfusion techniques involve the collection and reinfusion of the patient's own blood with PABD being the common used form[7-9].

Elective surgery in Orthopedics like spine or hip procedures is often associated with massive blood loss and high risk of anemia after surgery[6, 10, 11]. Delayed wound healing and infection could be related to anemia after surgery, and those are more susceptible and severe in orthopedics due to the implant. Additionally, anemia contributes to higher cardiac burden and may affect the functional exercise in the early postoperative period, which is essential for patients who underwent orthopedic surgery. With the development of the concept of enhanced recovery after surgery (ERAS) in recent years, better blood management to avoid anemia after surgery becomes increasingly important. In addition to an alternative in allogeneic blood shortage[12],

there are also other advantages about PABD. It can be used for patients with rare blood groups, multiple allo-antibodies or religious objections to allogeneic transfusion[13]. However, we should also be careful about this technique especially for the necessity, indication, and cost-effectiveness in the clinical practice[14]. PABD program should be a multidisciplinary issue and based on a discussion between doctor and patient regarding the procedure's risks and benefits.

Surgical procedures with high risk of allogeneic blood transfusion should be considered for PABD[9]. The less likely the transfusion, the more likely donated blood will not be used. Lumbar fusion surgery for patients with degenerative lumbar spine diseases often results in massive blood loss due to long time of operation, large wound and high difficulty to stop bleeding in the spinal canal area. All levels of anemia were reported to be significantly associated with prolonged length of hospitalization and poorer operative or 30-days outcomes in patients undergoing elective spine surgery.[15] Blood management could be essential especially for patients with spine deformity and long segments fusion. Kennedy et al. found that PABD was more efficient in patients who underwent instrumentation fusion but not all spine surgery[16]. Solves et al. also reported that PABD significantly decreased the allogeneic blood transfusion for spine instrumentation fusion in young patients[17]. However, it is still controversial about the appliance and effectiveness of PABD in spine surgery. Brookfield et al. reported that it is not beneficial for patients who underwent short lumbar spine fusion with normal blood coagulation[18]. Cohort study by Kelly et al. revealed that there is no protective effect of PABD against the risk of allogeneic blood transfusion for adult patients who underwent spine deformity surgery[19]. Moreover, evidence about the timing of blood donation in PABD program still remains insufficient[14, 20]. More evidence about the appliance and effectiveness of PABD in spine surgery is warranted.

In this randomized clinical trial, we aim to verify the clinical effectiveness of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery with respect to the incidence and number of allogeneic blood transfusion, hemoglobin (Hgb) decline, days of hospitalization after surgery, hematocrit level and incidence of complications. Study design of different time interval between blood donation and surgery help us to explore the optimal timing of autologous blood donation simultaneously.

METHOD

Study design

This study is planned to be a prospective and open-label randomized controlled trial with three groups. (**Figure 1**)

Recruitment and informed consent

This single-centre study will be conducted in the Peking University Third Hospital (PUTH). Eligible participants will be recruited from the patients who are going to receive lumbar fusion surgery in a three-years period from 01-Jan-2022 to 31-Dec-2024 by our researchers. Recruitment, assessment and randomization will be finished in the

Inpatient Management Centre (IMC) that is in charge of pre-operative evaluation before patients' admission. Researchers will discuss with eligible patients when they have decided to receive lumbar fusion surgery and then finish the informed consent. After enrolment, participants will be coded as a unique number and general information will be recorded.

Eligibility

Inclusion criteria

a. Patients who will receive elective lumbar fusion surgery for lumbar degenerative disease
b. Age between 18 and 70 years
c. Hgb over 110 g/L
d. "High risk" for the risk score of allogeneic blood transfusion for lumbar fusion surgery

Exclusion criteria

a. Diagnosed with malignant metastases
b. Infectious diseases
c. Cardiovascular and cerebrovascular diseases such as coronary heart disease and severe aortic stenosis
d. Hematological disorders or drug history which are not suitable for blood donation
e. Critically ill patients
f. Refuse to participate for any reason

Randomization

Eligible participants recruited from the IMC in PUTH will be randomized to three groups via random number method by researcher who is blinded for outcome collection. Patients in group A will not receive PABD and be regarded as control group. PABD will be performed for patients in group B and C. Blood donation will be finished at 1 week (±3d) before surgery in group B and 2 weeks (±3d) before surgery in group C. Randomization of the three groups will be on a 1:1:1 basis.

Blinding

Participants and surgeons will not be blinded to the interventions. As the PABD plans should be informed to patients clearly. The assessment after surgery will be performed by research assistants who are blinded to the recruitment and randomization.

Interventions

Blood donation and transfusion

All eligible participants will be randomized to three groups after pre-operative evaluation. Participants in group A will not receive PABD and regarded as control group. Donation of 400ml autologous blood will be finished once at 1 week (±3d) before surgery for participants in group B and 2 weeks (±3d) before surgery for group C. We also allow participants to finish the donation 3 days before or after the time

points in consideration of the feasibility in practice. All donated blood in our study will be transfused back during surgery unless the haemoglobin level is still above 125 g/L for male and 115 g/L for female before wound closure, then the autologous blood will not be transfused and be stored until the discharge of patients. Tranexamic acid and intraoperative blood salvage will be applied in three groups as usual. Autologous blood donation, preservation at 2 to 6 degree centigrade in dedicated refrigerator and transfusion during surgery will be assisted and finished by department of Blood Transfusion and Anesthesiology. Patients in group B and C will be given subcutaneous injection of 10000U erythropoietin (EPO) every other day (qod) until the date of surgery. Time schedule of interventions can be followed in the **Table 1**.

Table 1 Time schedule of interventions

Interventions	Admission	1-2 weeks before surgery	Peri-operation
Pre-operative evaluation	√		
Blood donation		√	
EPO injection		√	
Autologous blood transfusion			√

EPO, erythropoietin.

Assessment and management

We have established a risk score of allogeneic blood transfusion for lumbar fusion surgery in the preliminary study. This score system consist of six parameters including age, BMI index, number of fusion and fixation segments, spine deformity and Hgb level (**Table 2**). The risk score of allogeneic blood transfusion for lumbar fusion surgery was established based on the retrospective data of 5101 cases of lumbar spine surgery in the past two years from 2018 to 2019. We have performed preliminary validation for the risk score system in the patients from January to June 2020 prospectively. The effectiveness was acceptable with sensitivity of 76% (AUC=0.83).

All participants will be assessed at outpatient and IMC, including demographic information, height and weight, blood test and radiographic examination. Spine surgeons will make a general surgical plan including fusion and fixation segments. Patients with low risk of allogeneic blood transfusion will be excluded from our study. Baseline iron metabolism and vitamin will be screened for all participants. Oral iron supplements and vitamin drugs will be initialed and continued until the day before surgery for patients with iron and vitamin deficiencies. All patients will receive one unit of allogenic blood transfusion if their haemoglobin level drop below 8.0 g/dL and the patient display clinical symptom of anemia (tachycardia and/or hypotension) despite intravenous fluid boluses.

Table 2 Risk score of allogeneic blood transfusion for lumbar fusion surgery

Characteristic	Score
Age	
<60 years	0
≥60 years	1

BMI	
≥18.5	0
<18.5	1
No. of fusion segments	
1	1
2	2
3	3
≥4	4
No. of fixation segments	
2	1
3	2
4	3
≥5	4
Spine deformity	
No	0
Yes	1
Hemoglobin (g/L)	
≥140	0
125-140	1
<125	2

BMI, body mass index. Total score 0-4 = low risk; Total score 5-13 = high risk.

Outcome measurements

Primary outcome

Incidence of allogeneic blood transfusion

Intraoperative or postoperative allogeneic blood transfusion will be recorded as binary outcome. Incidence of allogeneic blood transfusion will be statistically compared as primary outcome.

Amount of allogeneic blood transfusion

Total number(ml) of allogeneic blood transfusion for each patient in three groups will be recorded as continuous outcome and analysed as the primary outcome.

Hgb decline

Hgb decline(g/L) from one day before surgery to one day before discharge will be recorded as continuous outcome and analysed as one of the primary outcomes.

Secondary outcome

Days of hospitalization after surgery

Length of hospitalization after surgery could be an indicator for recovery and will be recorded as continuous outcome in this study. Days of hospitalization after surgery will be compared and statistically analysed as secondary outcome.

Hematocrit level

Hematocrit check will be scheduled weekly for patients in group B and C. Pre-operative hematocrit level will be assessed in group A regularly. Initial and pre-operative hematocrit level will be compared between two groups receiving EPO administration and recorded as secondary outcome.

Incidence of complications

Wound infection and complications associated with blood transfusion will be recorded as binary outcome and analyzed as secondary outcome

Data management

Each patient will receive a unique number and all data will be recorded with this number. An attending spine surgeon and a research assistant will be in charge of the examination and assessment in the perioperative period. Research assistant will maintain the follow-up one month after surgery. Data entry and transfer will be performed by two staff and two computers. All data including baseline information, risk score, Hgb result, allogeneic blood transfusion and ability assessments will be secured in PUTH and the access will be restricted to the research team. Database will be established after finishing all the data collection and back-ups will be made in multiple disks. All raw data will be kept in the Medical record department.

Patient and public involvement

Patients or public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Safety monitoring and adverse events

Participants in this study will receive PABD before lumbar spine surgery. All participants will be observed for 40 minutes after blood donation. Patients with Hgb less than 110g/L, infectious diseases, cardiovascular or cerebrovascular diseases will be excluded from our study in consideration of safety. Strictly standard collection and storage processes will be performed and monitored by department of IMC and Blood Transfusion. All expected or unexpected adverse events from this study will be recorded and monitored. Patients suffered from any adverse events related to the interventions in research will receive free treatment.

Sample size calculation

There were 5101 cases of lumbar fusion surgery from Jan 2018 to Nov 2019 and 817 cases received allogeneic blood transfusion. The incidence of allogeneic blood transfusion was 16%. The preliminary study of PABD from Aug 2020 to Sep 2020 demonstrated that the incidence of allogeneic blood transfusion decreased by 18% compared with the same time period in 2019. We hypothesize that the incidence of

allogeneic blood transfusion decreased by 18% via PABD for patients at "high risk" score for lumbar fusion surgery. We should recruit 400 patients for both group PABD and non-PABD. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate and accuracy rate of 80% for risk score system. On the other hand, a single injection of EPO was reported to result in Hgb increase of 2.9g/L in adolescence[21]. We hypothesize that a single injection of EPO could attain Hgb increase of 2.5 g/L in adults who are going to receive lumbar fusion surgery, the Hgb level in group C before surgery should be 10 g/L more than patients in group B and we assume to be 120g/L and 110g/L, respectively. Then we should recruit 330 patients for both group B and C. This is based on α at 0.025 and power at 80% considering a 1:1 allocation rate. To sum up, we will recruit a total of 1200 patients for three groups.

Statistical analysis

The baseline characteristics of all participants will be summarized by group and presented as means (SD) for continuous variables, and count (%) for categorial variables. All the confounding variables which may influence the primary outcome will be recorded and compared among three groups. Incidence of allogeneic blood transfusion and complications will be measured as binary outcome. Amount of allogeneic blood transfusion (ml), Hgb decline, days of hospitalization after surgery and hematocrit level will be measured as continuous outcome. Chi-square test and logistical regression will be used for the binary outcome. Nonparametric test or t test will be performed for continuous outcome according to the distribution. A value of $P<0.05$ will be considered as statistically significant. All analysis will be performed using SPSS 17.0 by a researcher who is blinded to recruitment and data collection.

Ethic and dissemination

This trial has been approved by the Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02) and registered on Chictr.org (registration number: ChiCTR2000039824). Informed consent will be obtained for all participants. Results of the trial will be submitted for publication in a peer-reviewed journal and as conference presentations.

DISCUSSION

We have presented the rationale and design of a prospective randomized controlled trial to compare the outcomes of PABD in patients at high risk of allogeneic blood transfusion for lumbar fusion surgery. The RCT will compare the outcome among three groups to verify the clinical effectiveness of PABD and explore the optimal timing of blood donation with adjuvant EPO injection in lumbar fusion surgery.

In the previous studies of PABD, the time interval between first blood donation and surgery varied from less than 2 weeks to more than 4 weeks[14, 20]. Adequate time interval was thought to be crucial for the red blood cell (RBC) regeneration of donated blood[22]. But it should also be noted that there is an outdate for the donated blood in plastic bags. An appropriate time interval to balance the regeneration and preservation of donated blood is significant for the efficiency of PABD program. We choose an

interval of 1 to 2 weeks to reduce the storage time of donated blood in autologous blood bank. Meanwhile, adjuvant EPO injection after blood donation will be used for all patients in group B and C to accelerate the RBC regeneration. EPO injection was reported to be useful for increasing the RBC before hip surgery and avoiding allogeneic transfusion during spinal deformity surgery in PABD program[21, 23]. To explore the optimal timing of autologous blood donation with EPO injection is also one of the main goals in this prospective study.

In this study, a validated risk score system of allogeneic blood transfusion for lumbar fusion surgery based on retrospective study with large sample size will be implemented to ensure the necessity for PABD program. Both this technique and EPO injection should be more efficient in the patients with higher risk of blood transfusion[20, 24]. Waste of donated blood was an inherent risk for PABD program[25, 26]. The review by Singbartl et. al reported that the wastage of unneeded PABD units varied from 18% to above 50%[27]. All donated blood in our study will be storage for a relatively shorter time period and transfused back during operation unless the haemoglobin level is still above 125 g/L for male and 115 g/L for female before wound closure, then the autologous blood will not be transfused and be storage until the discharge of patients. This design aims to eliminate the waste of donated blood and simultaneously decrease the risk of allogeneic blood transfusion in peri-operative period for targeted patients who will receive lumbar fusion surgery. A multidisciplinary cooperation including department of IMC, Blood Transfusion, Anesthesiology and Orthopedics in the hospital will ensure the safety and feasibility of this prospective trial in clinical practice.

Contributors NX and YZ contributed to design the trial and drafted the manuscript. YT contributed to design the trial and oversaw the manuscript writing and submission. NX, YZ, YT, BL, HQ, XZ, NY, WL (Wei Li), CZ, WL (Weishi Li) and WF contributed to the trial design and have read and approved this manuscript.

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Competing interests None declared.

Patient consent No identifiable patient pictures or data have been involved in the protocol.

Ethics approval This trial has been approved by Peking University Third Hospital Medical Science Research Ethic Committee (No: 2020-262-02).

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure Legends

Figure 1 Study design

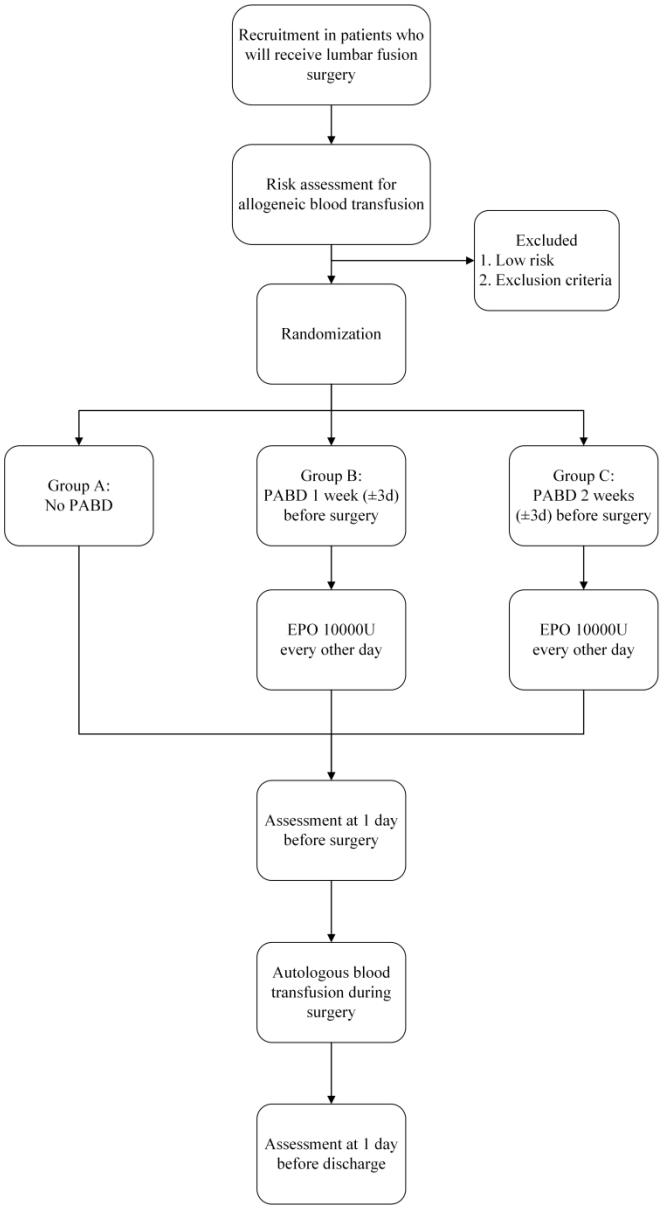

Figure 1 Study design

197x359mm (500 x 500 DPI)

Data availability statement

All data of the research, '**Prospective study of preoperative autologous blood donation for patients with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial**', will be secured in Peking University Third Hospital and the access will be restricted to the research team. Database will be established after finishing all the data collection and back-ups will be made in multiple disks. All raw data will be kept in the Medical record department. Reasonable request for data access could be directed to tiany@bjmu.edu.cn.

For "Prospective study of preoperative autologous blood donation for patient with high risk of allogeneic blood transfusion in lumbar fusion surgery: a study protocol of a randomized controlled trial"

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P2)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (√)
Funding	4	Sources and types of financial, material, and other support (P10)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P10)
	5b	Name and contact information for the trial sponsor (P10)
	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 (P10)
	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)
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 (P2-P3)
	6b	Explanation for choice of comparators (P3, P7-P8)
Objectives	7	Specific objectives or hypotheses (P3)

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, noninferiority, exploratory) (P3-P4)
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 (P5)
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) (P5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (P5-P7)
	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) (P8)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (P5-P8)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (P8)
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 (P7-P8)
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) (P6-P7)
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 (P9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P5)
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 (P5)
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 (P5 & P8)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (P5 & P8)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (P5)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (P5)
Methods: Data collection, management, and analysis		
Data collection methods	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 (P5-P8)
	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
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 (P8)
Statistical methods	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 (P9)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (P9)
	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) (P9)

Methods: Monitoring

Data monitoring	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 (P8)
	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
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 (P8)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P9)
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) (P9)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P10)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P8)
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 (P8)

Dissemination policy	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 (P8)
	31b	Authorship eligibility guidelines and any intended use of professional writers (P8)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.