



BMJ Open Safety of intravenous tranexamic acid in patients undergoing supratentorial meningiomas resection: protocol for a randomised, parallel-group, placebo control, non-inferiority trial

Shu Li ¹, Xiang Yan,² Ruowen Li,¹ Xingyue Zhang,¹ Tingting Ma,¹ Min Zeng,¹ Jia Dong,¹ Juan Wang,¹ Xiaoyuan Liu,¹ Yuming Peng ¹

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¹Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

²Department of Anesthesiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

Correspondence to

Dr Yuming Peng;
florapym766@163.com

ABSTRACT

Introduction Growing evidence recommends antifibrinolytic agent tranexamic acid (TXA) to reduce blood loss and transfusions rate in various surgical settings. However, postoperative seizure, as one of the major adverse effects of TXA infusion, has been a concern that restricts its utility in neurosurgery.

Methods and analysis This is a randomised, placebo-controlled, non-inferiority trial. Patients with supratentorial meningiomas and deemed suitable for surgical resection will be recruited in the trial. Patients will be randomised to receive either a single administration of 20 mg/kg TXA or a placebo of the same volume with a 1:1 allocation ratio after anaesthesia induction. The primary endpoint is the cumulative incidence of early postoperative seizures within 7 days after craniotomy. Secondary outcomes include the incidence of non-seizure complications, changes of haemoglobin level from baseline, intraoperative blood loss, erythrocyte transfusion volume, Karnofsky Performance Status, all-cause mortality, and length of stay, and total hospitalisation cost.

Ethics and dissemination This trial is registered at ClinicalTrials.gov and approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200224). The findings will be disseminated in peer-reviewed journals and presented at national or international conferences relevant to subject fields.

Trial registration number NCT04595786.

INTRODUCTION

Meningiomas are the most common intracranial tumours, accounting for over 30% of all intracranial neoplasms and resulting in severe neurological dysfunction.¹ Surgical resection of meningioma and its dural attachment is the preferred treatment strategy for either benign or malignant meningioma.² However, up to 21.6% of patients undergoing meningioma resection experienced excessive blood loss and life-threatening haemodynamic instability.^{3–4} Allogenic blood transfusion is associated with risks of transmitted infections,

Strengths and limitations of this study

- This is a randomised, parallel-group, placebo control, non-inferiority trial to evaluate the effect of a single administration of tranexamic acid (TXA) (20 mg/kg) on the cumulative incidence of early postoperative seizure (EPS) in patients under supratentorial meningioma resections.
- This study adopts uniformed TXA infusion dose, standardised randomised and blind, clear-cut inclusion and exclusion criteria, a rigorous anaesthesia management protocol, and experienced investigators in each key procedure of intervention and follow-up.
- One limitation of the study is it is a single-centre trial. Future multi-centre trial is needed to evaluate the effect of a single administration of TXA on the cumulative incidence of EPS in patients under supratentorial meningioma resections.
- Certain patients with known high risk for early postoperative complications are excluded for the safety concerns, including patients with preoperative seizures, history of thrombotic disease and chronic kidney disease.

postoperative sepsis and immune modulation.^{5–6} Hence, further strategies that minimise intraoperative bleeding are still in urgent need.

Tranexamic acid (TXA), an antifibrinolytic drug widely used for haemostasis, inhibits plasminogen activation and stabilises the blood clot by reversibly binding to the lysine residues on plasminogen, hence reducing intraoperative bleeding.⁷ TXA is used as a bolus ranging from 10 to 50 mg/kg, followed by a continuous infusion ranging from 1 to 5 mg/kg/hour until the end of the procedures in a variety of neurosurgical procedures.^{3–8–10} Unfortunately, the risk of postoperative seizures remains uncertain, and restricts the routine use of TXA in



neurosurgery, though it is a safe and effective means to reduce operative blood loss and blood transfusion rates in cardiac, pulmonary, trauma, obstetric, spinal and orthopaedic surgery.^{11–14}

As a synthetic lysine analogue, TXA can modify brain network excitability by activating excitatory ionotropic glutamate receptors.^{15 16} On the other hand, TXA may induce hyperexcitability by blocking gamma-aminobutyric acid-driven inhibition of the central nervous system.¹⁷ The competitive antagonism of glutamate receptor and gamma-aminobutyric acid may serve as a plausible explanation for the association between TXA and postoperative seizures. Moreover, inevitable disruption of the blood–brain barrier (BBB) and BBB permeability facilitate the entry of TXA into the central nervous system.¹⁸ Therefore, neurosurgical patients are probably at higher risk of postoperative seizure.

The postoperative seizure was reported in 11.0%–26.2% meningiomas resection patients, and among which, about 30%–40% were early postoperative seizure (EPS) occurred within 7 days after surgery.^{19–21} History of epilepsy, tumour recurrence, frontoparietal location and peritumoral oedema was reported to be associated with EPS.^{20 22 23} However, there is no prospective study focusing on the effect of tranexamic acid on EPS in patients undergoing meningioma resections, though TXA was proved of reducing intraoperative haemorrhage volume in traumatic brain injury surgery, paediatric craniostylosis surgery and meningioma resection.^{10 24 25}

Previously, an observational study reported the incidence of postoperative seizure in complex skull base neurosurgical procedures receiving intraoperative TXA was 3.3% (8/245), similar to patients without TXA infusion (2.2%, 6/274).⁸ However, the heterogeneity in histopathology and surgical approaches, the skull base location, as well as the study design, impede the generalisability of the results. A few randomised studies reported the difference in postoperative seizure fit in TXA treated patients and placebo-treated patients. Hooda *et al.*³ reported lower incidence in the TXA group compared with the placebo group in intracranial meningioma (3.3% vs 6.7%) patients while in other randomised controlled trials of paediatric craniostylosis and tumour resection, no seizures were observed.^{9 10 26} Nevertheless, the incidence of seizure attacks was measured as the secondary outcome and the sample size of both studies was relatively small.

Therefore, we design a randomised, placebo-controlled, non-inferiority trial, aiming to evaluate the effect of a single administration of TXA (20 mg/kg) on the cumulative incidence of EPS in patients undergoing supratentorial meningioma resections. In this study, we hypothesise that compared with the placebo group, the intraoperative, prophylactic use of TXA will not be inferior to the placebo group, regarding the cumulative incidence of EPS in patients receiving supratentorial meningioma resections.

METHODS

The protocol has been prepared according to Standard Protocol Items: Recommendations for Interventional Trials.²⁷ All trial procedures are summarised in [table 1](#). For completed checklists, see online supplemental file 1.

Study design

This is a randomised, parallel-group, placebo control, non-inferiority study to determine whether TXA increases in-hospital EPS in patients with supratentorial meningiomas. Supratentorial meningioma participants will be recruited from Beijing Tiantan Hospital, Capital Medical University from 2020 to 2022. This trial was approved by the Chinese Ethics Committee of Registering Clinical Trials on 31 August 2020 (reference number: ChiE-CRCT20200224) and registered in www.clinicaltrials.gov. Preoperative interviews will be conducted by specially trained research assistants who will inform patients about the study objectives, risks and benefits, and obtain written informed consent from participants or his/her legal representatives. [Figure 1](#) shows the flow chart of the study.

Population

Inclusion criteria

Patients scheduled to undergo elective supratentorial meningioma resections will be recruited for screening eligibility 1 day before surgery. Inclusion criteria include age between 18 and 80 years, and American Society of Anaesthesiologist physical status I to III.

Exclusion criteria

Patients will be excluded if they are allergic to TXA, with the onset of preoperative seizures, history of thrombotic disease and chronic kidney disease (glomerular filtration rate <60 mL/min or albumin–creatinine ratio >30 mg/g),²⁸ breast feeding, pregnancy or refusal to participate in the study.

Randomisation and blinding

Block randomisation (block size of 4 or 6) will be applied via a computer-produced randomised controlled table. Patients will be randomised within 24 hours before surgery. An independent research assistant will pack the allocation sequence with opaque, sealed, stapled envelopes and distribute them to the research nurse. The research nurse will prepare the drug for administration into a 50 mL syringe labelled ‘research agent’. Patients will be randomly allocated to TXA or placebo group in a 1:1 ratio.

The anaesthesiologists, neurosurgeons and endpoint assessors will all be blinded to the grouping until the completion of the study analysis unless specific circumstances, including the occurrence of a serious adverse event. The enrolled patients and their legal representatives will also be blinded to the research treatment.

Interventions

Patients will be randomly assigned into the TXA and the placebo groups. A reliable peripheral venous access will

Table 1 Schedule of enrolment, intervention and assessment

Study period		Allocation		Post-allocation		Follow-up			
Timepoint	Enrolment	Preoperation	After evaluation	Intraoperative	PACU	24 hours after operation	3 days after operation	7 days after operation	180 days after operation
Enrolment									
Eligibility screen	✓								
Informed consent	✓								
Allocation									
TXA group		✓							
Placebo group			✓						
Assessment									
Baseline variables									
Brain imaging	✓					✓			
Early postoperative seizure fit*					✓	✓	✓	✓	
Late seizure fit									
Intraoperative data				✓					
Estimated blood loss				✓					
Haemoglobin concentration	✓			✓					
Transfusion volume				✓					
Simpson grade				✓					
Blood gas and clotting function				✓					
KPS scale	✓							✓	✓
Postoperative complications					✓		✓	✓	✓
Length of stay and cost								✓	✓
ICU stay and length								✓	✓
All-cause mortality								✓	✓

*Primary outcome. ICU, intensive care unit; KPS, Karnofsky Performance Status; TXA, tranexamic acid.

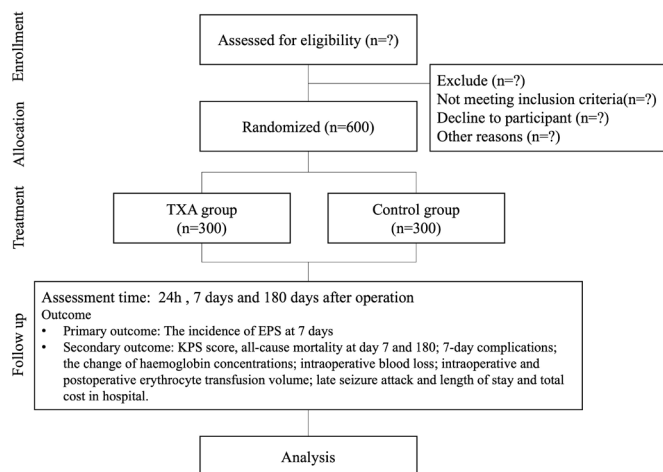


Figure 1 Consolidated Standards of Reporting Trials flow diagram. EPS, early postoperative seizure; KPS, Karnofsky Performance Status; TXA, tranexamic acid.

be established on arrival in the operation room. The TXA (20 mg/kg) will be diluted into a 50 mL syringe by a research nurse. After anaesthesia induction, patients in the TXA group will receive the single administration of TXA at a rate of about 150 mL/hour by the chief anaesthesiologists who are blinded to allocation. The TXA dosing regimen is mainly based on previous observational studies and small randomised trials focusing on intraoperative blood loss and perioperative blood transfusion.^{3 8 9} In the placebo group, the same volume of 0.9% saline will be administered at the same infusion rate. The chief anaesthesiologist blinded to the grouping will administer the investigated agent.

Standard anaesthesia management

Standard monitoring will include ECG, non-invasive blood pressure, heart rate, pulse oxygen saturation, invasive arterial pressure monitoring, end-tidal carbon dioxide, exhaled anaesthetic concentration, bispectral (BIS) index, temperature and urine output. All patients will be premedicated with midazolam (0.05 mg/kg) intravenously 5 min before anaesthesia induction. Anaesthesia will be induced with sufentanil (0.3–0.4 µg/kg), propofol (1.5–2.5 mg/kg) and rocuronium (0.9 mg/kg) or cisatracurium (0.2 mg/kg). After tracheal intubation, mechanical ventilation will be performed with the following parameters: tidal volume of 6–8 mL/kg, respiratory rate of 12–15/min, inspiration/expiration (I:E) ratio of 1:2, 50% inspired oxygen fraction and 50% and fresh gas at a flow rate of 1–2 L/min to maintain normocapnia.

Anaesthesia will be maintained with combined intravenous anaesthesia and inhalation anaesthesia. Along with the inhalational anaesthesia maintained with 0.5 minimum alveolar concentration, infusion of remifentanyl (0.1–0.2 µg/kg/min) and propofol (3–8 mg/kg/hour) will be maintained to keep BIS values between 40 and 50.

Intraoperative mean arterial pressure will be kept between $\pm 20\%$ of the baseline value. Cell salvage will be

used when estimated blood loss is >500 mL.²⁹ Allogeneic erythrocyte transfusion will be carried out for patients with haemoglobin lower than 70 g/L, or lower than 80 g/L in patients with cardiovascular disease, acute ischaemic stroke or under acute intraoperative bleeding.³⁰ Other blood products, including fresh frozen plasma, platelets, cryoprecipitate and prothrombin complex concentrate will be infused according to the blood transfusion guideline.³¹ Fluid input and output will also be closely monitored and recorded.

Patients will receive intravenous prophylaxis sodium valproate or levetiracetam after tumour resection and oral administration for 1 month if no epilepsy fit occurred and 1 year if seizure presented.

Data collection and measurement

The baseline seizure will be evaluated by neurosurgeons and neurologists before surgery, based on the International League Against Epilepsy (ILAE) operational definition of epilepsy.³² EPS will be defined as a new postoperative seizure fit within 7 days.^{33 34} All patients will receive brain imaging, including CT and MRI to assess the tumour size, location, vascularisation and oedema before surgery. The physiological parameters, the total doses of anaesthetics, coagulation, arterial blood gas analysis, estimated blood loss and blood transfusion will be recorded by anaesthesiologists through a designed data collection table. Simpson grading system will be used to describe the extent of meningioma resection.³⁵ All patients will receive brain CT scan 6 hours after operation to detect intracranial haematoma, cerebral oedema or newly onset stroke. The functional status will be assessed using Karnofsky Performance Status (KPS) at admission and 7 days and 180 days after surgery. Postoperative complications (defined in online supplemental table 1) and all-cause mortality will also be recorded. Long-term follow-up will be performed through telephone or a remote video interview to collect information.

Study objectives

The study aims to demonstrate the non-inferiority of intravenous administration TXA in cumulative EPS incidence after neurosurgery, and hence to investigate the safety of TXA on seizure in neurosurgical procedures. The assessment of primary and secondary outcomes will be performed by trained research assessors blinded to the group allocation.

Primary endpoint

The primary endpoint is the cumulative incidence of EPS, defined as a transient occurrence of involuntary movements, abnormal sensory phenomena or an altered mental status that could not otherwise be explained within 7 days after surgery.²¹ If an EPS could not be diagnosed on clinical grounds alone, acute electroencephalograms (EEG) will be performed within 24 hours of event occurrence to confirm the diagnosis. If the EEG showed evidence of interictal or seizure activity, the event will be

defined as EPS. If EEG was not done within 24 hours or if the EEG findings were not diagnostic, the event was classified as no EPS. EPS will be recorded by the neurosurgeons, intensive care staff, care workers, and documented in the medical records. Classification, duration and treatment of seizure fit will also be evaluated by trained neurosurgeons and neurologists blinded to allocation. Clinical, laboratory and cerebral CT after newly onset of EPS will be recorded to rule out intracranial bleeding, stroke, severe cerebral oedema or other intracranial pathologies. The types of attacks will be classified according to the classification of ILAE.³⁶

Secondary endpoints

The secondary endpoints include the following:

- ▶ The incidence of complications within 7 days after the intervention, including intracranial haematoma, deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, stroke, myocardial infarction, acute kidney infarction, anaemia and infection. The severity and nature of complications will be graded with the Landriel classification of complications in neurosurgery.³⁷
- ▶ The changes in haemoglobin concentrations between baseline and end of surgery.
- ▶ Intraoperative blood loss evaluated using the formula³⁸:

Estimated intraoperative blood loss=collected blood volume in the suction canister (mL)–volume of flushing (mL)+volume from gauze tampon (mL).

- ▶ The intraoperative and postoperative (within 7 days after surgery) erythrocyte transfusion volume.
- ▶ The KPS score at 7 days and 180 days after the operation.
- ▶ All-cause mortality at day 7 and 180 days after surgery.
- ▶ The late occurring seizure attacks (after 7 days) during follow-up.
- ▶ The length of hospital stays and total hospitalisation cost.

Data Monitoring Committee

The project will be monitored by the Data Monitoring Committee (DMC) composed of specialists in anaesthesiology, neurosurgery, ethics, statistics and methodology. The DMC will audit through regular interviews or telephone calls and be responsible for terminating the research in case of severe adverse events.

Statistical analysis plan

All outcomes will be analysed according to the statistical analysis plan with STATA V.15.0 (StataCorp). The data will be analysed according to both the intention-to-treat (ITT) and per-protocol (PP) approach. Non-inferiority may be declared only if both analyses support the same conclusion. The ITT analysis will depend on the allocated population while the PP analysis will depend on the actual treatment the participants receive. Continuous data will be reported as means with SD and medians with

IQR for normally distributed and skewed data. Categorical data will be presented as counts (percentage). The differences of the primary outcome will be compared between groups using χ^2 analysis. The primary outcome will be analysed in the following subgroups: age, gender, peritumoral oedema, tumour site, tumour volume. The cumulative incidence of EPS will also be adjusted for either imbalanced or prognostic baseline covariates using logistic regression model. Other categorical variables will be analysed by χ^2 test or Fisher's exact test and continuous variables using Student's t-test or Mann-Whitney U test. Besides, missing data will be imputed using inverse probability weighting and the worst-case imputation scenarios. The statistical significance will be declared at a type I error of 0.05.

Sample size calculation

The PASS 11 software (NCSS, LLC, USA) was used to calculate the sample size based on the cumulative incidence of EPS after supratentorial meningioma resection. Several trials focused on postoperative seizure attacks in meningioma patients; however, only a few reported the incidence of EPS in preoperatively seizure-free patients at the early postoperative stage. In a retrospective study of seizure in supratentorial meningioma resection, EPS attacks were observed in 4.83% (34/704) preoperative seizure-free participants.²² In another observational study, postoperative new seizures were observed in 104 (19.4%) cases of preoperative seizure-free patients, and among them, 46 (8.6%) cases had EPS.²⁰ Another study also reported an incidence of 6.4% (14/218) for EPS in preoperative seizure-free meningioma participants.²¹ On the other hand, in an observational study carried out in our institution, the incidence of EPS for supratentorial meningiomas resections was only 3.8% (26/678).¹⁹ Therefore, we assume that the incidence of EPS in preoperative seizure-free meningioma patients is 6.0%. In the meta-analysis of TXA associated seizure and infusion dose, patients receiving lower (<45 mg/kg) doses of TXA had 6.3 times the odds of postoperative seizure, compared with those in the placebo group. The absolute difference between the TXA group and placebo group was 22%.³⁹ Therefore, a non-inferiority margin of 5.5% in EPS is set in the analysis for the cumulative incidence between the two groups (TXA group minus placebo group). The TXA group will be declared non-inferior to the placebo group if the upper limit of 95% CI for the difference in EPS incidence is below the non-inferiority margin of 5.5%. A sample size of 600 patients (300 per group) will ensure this non-inferiority of the TXA group to achieve a power of 80% at a one-side α of 0.025, with a dropout rate of 2.5%.

Reporting of adverse events

All adverse events associated with the trial will be recorded and closely monitored until a stable situation or stabilisation has been reached, or it has been proved that TXA is not the cause of the event. The principal investigator

is responsible for reporting all adverse events. Once an adverse event occurs, it should be immediately reported to the research department and the investigator to determine the severity of the adverse event. All adverse events associated with this study will be recorded and reported to the Ethics Committee within 24 hours. The blind will be broken for severe adverse events submitted to the primary investigator, Ethics Committee, and all participating investigators.

Data management

All collected data will be kept strictly confidential for research purposes only. The paper case report form and electronic data collection form will be used at the same time. Files containing information from the participants will be stored in a locked filing cabinet at the Department of Anaesthesiology, Beijing Tiantan Hospital. The data will be stored in a research computer and backup will be performed on a weekly basis on another external hard drive.

Protocol amendment

The principal investigator will be responsible for any decision to amend the protocol that may impact the potential safety and benefits to the patients or conduct of the study. If there is any modification (eg, changes to population, sample sizes, study procedure, interventions, outcomes or analyses), the principal investigator will communicate with relevant parties and gain approval from the China Ethics Committee of Registering Clinical Trials before implementation.

Ethics and dissemination

The study was approved by the Chinese Ethics Committee of Registering Clinical Trials on 31 August 2020 (reference number: ChiECRCT20200224). The study recruited the first patient on 30 October 2020, and the study is estimated to be completed on 30 September 2022. The findings of the study will be disseminated in peer-reviewed journals and will be presented at national or international conferences.

DISCUSSION

This is a randomised, parallel-group, placebo control, non-inferiority trial aiming to investigate the effect of prophylactic use of TXA on the incidence of EPS in adult patients after meningiomas resection. Our primary hypothesis is that 20 mg/kg TXA would be non-inferior to normal saline in terms of postoperative 7day seizures.

The optimal dosage of intravenous TXA for reducing intraoperative bleeding is unknown. A meta-analysis reported that a total dose of 20 mg/kg TXA was sufficient to reduce blood loss, and a higher TXA dose (>20 mg/kg) would not gain further benefit in cardiac surgery.⁴⁰ Meanwhile, another meta-analysis showed that a single infusion of TXA (10–20 mg/kg) could reduce intraoperative bleeding by 153 mL and decrease transfusion rates by

72% in orthopaedic, obstetrics and gynaecology surgery, with the dose-dependent effect.⁴¹ In previous neurosurgical studies aiming to investigate efficacy and safety of TXA, the initial administration dose ranged from 10 to 25 mg/kg, and the maintenance dose ranged from 1 to 10 mg/kg/hour, with no thrombosis-related adverse event was observed.^{9 26} Moreover, a recent cranioclysis randomised controlled study¹⁰ found that followed by the same maintenance dose (5 mg/kg/hour), the low TXA loading dose (10 mg/kg) was non-inferior to the high loading dose (50 mg/kg) in decreasing blood loss and transfusion requirements. Therefore, we adopted the single infusion of 20 mg/kg TXA as our intervention to ensure efficacy in reducing haemorrhage and safety in postoperative seizures.

Acute electroencephalograms will be ordered in cases in which the diagnosis of an EPS is dubitable.²¹ By reviewing electroencephalograms, brain images (CT or MR scans) ordered for detecting intracranial conditions as well as clinical and laboratory data when EPS occurs, we can identify the likely cause of seizure attacks and other conditions that can cause seizure-like activity, including coma, vegetative state, and syncope.

In previous observational studies, age, location and peritumoral oedema were reported to be associated with increased odds of perioperative seizure. In addition, the study of EPS in patients undergoing brain tumour surgery indicated tumour compression of epileptogenic brain tissues is another risk factor for EPS.⁴² Moreover, prior work reported tumour size and sex have been associated with the risk of preoperative and postoperative seizures in meningioma patients.^{20 22 43} To approach a valid estimate of the cumulative incidence of EPS, we will perform subgroup analysis by age, sex, peritumoral oedema, tumour site and tumour size. Therefore, a prospective, randomised, controlled, non-inferiority trial is required to account for the perioperative confounders and demonstrate the safety of TXA on early post seizures for patients undergoing meningioma resections.

The present study features involve uniformed TXA infusion dose, standardised randomised and blind setting, clear-cut inclusion and exclusion criteria, a rigorous uniform protocol to manage intraoperative haemodynamic, respiratory parameters, body temperature, and experienced anaesthesiologists, neurosurgeons, and neurologists in each key procedure of intervention and follow-up. This is the first study to evaluate the impact of TXA on EPS in neurosurgical patients to the best of our knowledge. The findings of this study will help to provide references for the safe use of TXA in patients undergoing neurosurgery.

Patient and public involvement

Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, recruitment and conduct of the study. At the completion of this trial, a manuscript will be prepared to present the

trial results. Results of the final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrolment. The burden of intervention will not be taken by participants themselves.

Contributors SL and XY conceived the study. SL, MZ and YP initiated the study design and helped with protocol development and implementation. SL, XY, RL, XZ, TM, MZ, JW, JD, XL and YP helped in data collection and manuscript revision. YP is the grant holder. SL and XY are the cofirst authors. YP is the responsible author. All authors contributed to the refinement of the study protocol. All authors have read and approved the final.

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ORCID iDs

Shu Li <http://orcid.org/0000-0002-5625-067X>

Yuming Peng <http://orcid.org/0000-0002-2630-2467>

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