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Effect of tranexamic acid on the prognosis of patients with traumatic brain injury undergoing craniotomy: study protocol for a randomized controlled trial

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Abstract

Introduction Abnormal coagulation function aggravate the prognosis of patients with traumatic brain injury (TBI). It was reported that the anti-fibrinolytic drug tranexamic acid (TXA) could reduce intracranial hemorrhage and mortality in non-operative TBI patients. However, there is a lack of evaluation of TXA in TBI patients undergoing craniotomy.

Methods and analysis This is a single-centre randomized controlled, double-blind, parallel study aiming to investigate the effectiveness and safety of TXA in TBI patients during the perioperative period. Neurological function, mortality, adverse events, blood loss and transfusion, serum immune-inflammatory cytokines will be collected and analysed.

Ethics and dissemination Ethical approval has been granted by the Medical Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University (reference number: KY 2020-136-03). The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Trial registration number ChiCTR2100041911.

Strengths and limitation of this study

- This is a randomized controlled, double-blind, parallel study to test the hypothesis that TXA could improve the prognosis of TBI patients undergoing craniotomy.
- The study will provide evidence for optimizing the perioperative treatment of TBI patients undergoing craniotomy.
- There are nearly seven hundred cases of TBI patients that need neurosurgery every year at Beijing Tiantan Hospital, Capital Medical University. It is feasible and reasonable to complete the trial in 2 years.
- The study may not be generalized to other populations since it is a single-centre trial.

Key words Traumatic brain injury; Traumatic coagulation disorder; Tranexamic acid; The inflammatory response

Introduction

About 1.5 million people die each year from traumatic brain injury (TBI), which has

become the leading cause of death and disability worldwide. Brain tissue injury and hemorrhage are the main clinical manifestations of TBI. Systemic inflammatory reaction and abnormal coagulation function after TBI can cause secondary brain injury and aggravate cerebral hemorrhage, which has extremely adverse effect on the prognosis.

In recent years, many studies have shown that abnormal coagulation function is common in TBI patients and is one of the main causes of secondary brain injury. The incidence of coagulation dysfunction on admission is about 26% in TBI patients, and over 60% of them with severe TBI[1]. A prospective study found that TBI patients with abnormal coagulation function had a 4.7-fold increase in mortality and an increased risk of poor prognosis compared with those without abnormal coagulation function[2]. Some studies have confirmed the interaction between abnormal coagulation function, hyperfibrinolysis and systemic inflammatory reactions.

Tranexamic Acid (TXA) have anti-fibrinolytic and anti-inflammatory effect. Studies have reported that early use of TXA can reduce blood loss and mortality in TBI patients with non-surgical treatment [3, 4]. Some studies[5-9] suggested that the use of TXA could reduce the mortality and disability of the TBI patients and probably does not increase the risk of adverse events. TXA may be a potential treatment for TBI patients.

It is generally believed that the abnormal coagulation function after TBI is closely related to the degree of brain tissue damage. Studies have shown that more than 60% of patients with severe TBI are accompanied by abnormal coagulation function [1]. The incidence of abnormal coagulation function is increased in TBI patients combined with systemic injury compared with simple TBI patients[10].

Kearney et al have found that the patients with penetrative TBI, compared with non-penetrating TBI patients, have a higher mortality rate and a higher degree of abnormality in Glasgow Coma Scale (GCS), Simplify acute Physiological Score (SAPS) and Disseminated intravascular coagulation (DIC)[11]. However, TBI patients requiring craniotomy for hematoma removal are almost those with severe craniocerebral trauma, who is complicated by severe systemic inflammatory response and coagulation dysfunction. It is not clear, that for emergency TBI patients who need craniotomy, whether the use of TXA can improve the prognosis. It still needs further research to determine the effect of TXA on the systemic inflammatory reaction and coagulation function in TBI patients who received craniotomy procedures.

To sum up, this study intends to evaluate the efficacy and safety of intravenously administration of TXA in TBI patients undergoing craniotomy procedures. We also aim to explore the impact of TXA on systemic inflammatory response and coagulation function of the patients, and the relationship between these effects and the prognosis. This study will provide the basis for further development of perioperative TXA usage in TBI patients and optimize the perioperative treatment plan for TBI patients.

Methods

Study design

This study is a single-centre randomized double-blind placebo-controlled parallel study.

Objectives

This trial aims to investigate the effect and safety of TXA in TBI patients during the perioperative period.

Inclusion criteria

TBI patients aged ≥ 18 years and ≤ 65 years who scheduled to receive craniotomy hematoma removal surgery in Beijing Tian Tan Hospital，Capital Medical University from 2021 to 2023 will be recruited consecutively for eligibility screening.

Exclusion criteria

Patients will be excluded if they have the circumstances below: allergic history to TXA; using thrombin; taking anticoagulants; consumptive coagulation disorder; history of thrombosis (deep vein thrombosis, pulmonary embolism, cerebral thrombosis, myocardial infarction, thrombophlebitis); renal insufficiency; pregnancy; epilepsy; mental illness.

Randomization and blinding

We will prepare TXA and saline injections in the same colorless and transparent packaging. A full-time quality control person not involved in clinical treatment shall be set up. This person will pack the injections into opaque envelopes blindly, with one drug corresponding to one number. Each envelope includes: eight TXA (250mg/5ml) injections or eight 0.9% saline injections and one sterile 50ml syringe. After the patient signs the informed consent form and enters the operating room, the anesthesiologist will inform the quality control person to generate the random sequence through the computer and obtain the sealed envelope with corresponding number. Ensure that treatment information is concealed from anesthesiologists, nurses, surgeons, and the follow-up staff.

Grouping

According to whether TXA is used or not, patients will be randomly divided into TXA treatment group (TXA group) and placebo group (P group).

Intervention

The TXA group will be given TXA 2g (40ml). The P group will be given a placebo (0.9% normal saline, 40ml). After the patient is routinely monitored in the operating room and the peripheral vein is established, injections will be pumped at the rate of 80ml/hour for 15min (loading dose, 1g), and then 2.5ml/hour until the injection is completed (maintenance dose, 1g for 8h).

Anesthesia management

Standardized procedure will be applied. After the patient enters the operating room (room temperature is 24 ℃ ~ 26 ℃), non-invasive blood pressure, electrocardiogram, pulse blood oxygen, anesthesia gas monitoring and body temperature will be routinely monitored. The experimental drugs are pumped intravenously according to groups. Induction drugs include sufentanil (0.3 ~ 0.4 mg/kg), etomidate (0.3~ 0.4 mg/kg), and rocuronium (0.6 mg/kg). After induction, endotracheal intubation is followed and the respiratory parameters are adjusted to maintain PCO2 within physiological range (35-45 cmH2O). Arterial and central venous catheterization will be established. Intraoperative anesthesia will be adjusted with propofol (2 ~ 6 mg/kg/hour), remifentanil (0.1~0.2 mg/kg/min) and sevoflurane (0.5~1%) to maintain the MAP ≥

60mmHg, and muscle relaxants will be added when necessary. After the operation, the tracheal catheter will be kept or removed(depending on circumstances of patients) and patients will be transferred to intensive care unit (ICU) or neurosurgical ward.

Patient and public involvement

Patients and the public will not be involved in the development of the research question or the design of the study. Study results will be disseminated by publication in a medical journal and poster presentation at a medical conference.

Primary outcome

The primary outcome is the Glasgow outcome scale-extended (GOSE) [12]at discharge. GOSE includes 8 categories: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery. Good interrater reliability and content validity have been demonstrated for the GOSE in clinical outcome evaluation in TBI patients.

Secondary outcome

- 30-day mortality rate after surgery.
- Thrombotic events during hospitalization: include myocardial infarction, pulmonary embolism, deep vein thrombosis, and cerebral infarction.
- Perioperative blood loss: blood loss during the operation and the postoperative drainage in ICU and ward
- Blood transfusion: blood transfusion during the operation and postoperatively in ICU and ward, including red blood cells, fresh frozen plasma, fibrinogen and platelets.
- Incidence of postoperative infection: include pulmonary infection, incision infection, intracranial infection and urinary system infection.
- Hospitalization mortality rate.
- Length of hospitalization.
- Hospitalization costs.
- Coma Recovery Scale score-Revised (CRS-R) [13]at discharge: CRS-R will be applied to assess the quality of recovery of the TBI patients at discharge.
- Biomarkers: 3ml blood will be collected from the patients before, 1 day and 7 days after surgery. Blood will be centrifuged for 3000 rotation for 10 minutes, and the supernatant is collected and stored at -80 °C. Serological tests include: Traumatic stress index: Adcorticotropic hormone (ACTH), adrenaline (AD), Norepinephrine (NE), cortisol, lactic acid. Immune inflammatory factors: Human monocyte chemotactic protein-1 (McP-1), tumor necrosis factor-α (TNF-α), C reactive protein (CRP), peripheral blood leukocyte count and classification, interleukin-1, IL-6, and IL-10.

Follow-up

Clinical prognosis of postoperative outcomes will be collected through telephone or interview 30 days and 3 months after discharge, including acute cerebral ischemia, cerebral hemorrhage, dominant stroke, transient ischemic attack, death, myocardial infarction, non-fatal myocardial injury, major cardiovascular adverse events, hemorrhage, new onset atrial fibrillation, hypotension, congestive heart failure, new

onset acute renal failure and infection.

Sample size estimates

We used the PASS 2008 software (NCSS LLC, USA) for Windows to calculate the sample size. Based on our previous retrospective studies, the severe disability (Glasgow outcome score 1~3) rate undergoing craniotomy hematoma removal was 54%. The sample size was calculated with the model of Test for Two Means [Differences] in PASS V.11 software (NCSS, Kaysville, Utah, USA) on the basis of the anticipated the severe disability rate to reduce by 15% (54% to 46%). Given an alpha level of 0.05, a beta level of 0.2, the total sample size required is 613 in each group. Therefore, 1226 patients will be enrolled in this study.

Statistical plan

STATA statistical software will be used. Quantitative data variables will be expressed as mean ± standard deviation, quantitative data with non-normal distribution are expressed as median (interquartile interval), and qualitative data use cases (percentage). For continuous data, the normality test will be performed first. If each group meets the normality and the variance between the two groups is equal, the T-test will be used for comparison between groups. Otherwise, non-parametric Wilcoxon rank sum test or Mann-Whitney test will be considered. For the classified data, the chi-square test or Fisher's exact probability test will be used for the unordered outcomes, and the non-parametric Wilcoxon rank sum test for the ordered data. For statistical analysis, GOSE 1-4 will be defined as unfavorable outcome, GOSE 5-8 are defined as favorable outcome. Multivariate regression analysis will be used to evaluate the primary outcome. Multivariate analysis and linear regression will be used to evaluate the relationship between the outcome indicators.

Adverse Events

All study-related adverse events will be closely monitored, and details such as the nature, severity, and treatment will be recorded on the CRF until they are resolved, and the patient is stable. Whenever an adverse event occurs, it will be reported to the principal investigator immediately, and the severity, cause and consequences will be determined. All adverse events will be compared between the groups using the chi-square test or Fisher’s exact test.

Discussion

This study is a single-centre randomized double-blind placebo-controlled parallel study. To evaluate the influence of perioperative intravenous TXA treatment on the prognosis of TBI patients undergoing craniotomy for hematoma removal after emergency admission to Beijing Tian Tan Hospital. We also want to explore the influence of TXA on perioperative coagulation function and systemic inflammatory response of patients and its relationship with prognosis.

The World Health Organization has declared TBI to be the leading cause of death and disability worldwide by 2020[14]. Cerebral hemorrhage is the main clinical manifestation of TBI, and traumatic coagulation disorder is the main cause of progressive aggravation of cerebral hemorrhage. Studies have reported that the incidence of abnormal coagulation function after TBI is 35.2 % (29.0 % - 41.4 %), and

the mortality rate of patients with simple TBI complicated with abnormal coagulation function is 17-86 % [15]. Compared with TBI patients without coagulation dysfunction, the mortality rate of TBI patients with coagulation dysfunction is 4.7 times higher, and the risk of poor prognosis is also increased[2]. The abnormal coagulation function after TBI is directly related to the degree of brain tissue damage[11]. In addition, systemic inflammatory response after TBI can aggravate coagulation dysfunction in TBI patients, which is one of the important causes of secondary brain injury [16].

Studies suggest that the main mechanism leading to abnormal coagulation function after TBI is the activation of tissue plasminogen, hyperfibrinolysis, and disruption of the balance between coagulation and bleeding[17]. After severe TBI, a strong stress response occurs, which then induces systemic inflammatory response syndrome, leading to increased bleeding, increased blood transfusion, systemic organ failure, aggravating patients' abnormal coagulation function, and resulting in increased mortality [18, 19]. In addition, excessive consumption of coagulation factors and platelet dysfunction[20], hypoperfusion and protein-C pathway activation, hypothermia, metabolic acidosis, and hemodilution can also lead to coagulation dysfunction after TBI [21]. In TBI patients, the blood-brain barrier is destroyed, fibrinogen and its degradation products enter the brain, activate the inflammatory reaction cascade and the immune response in the brain, leading to lymphocyte infiltration, glial cell activation, cytokine release and reactive oxygen element production in the brain. These lead to axonal demyelination and neuronal damage[22]. Therefore, abnormal coagulation function significantly increases the mortality of patients, the regulation of patients' coagulation function has great clinical significance for improving the prognosis of patients, which has attracted more and more attention.

TXA is an anti-fibrinolytic drug that competitively binds to the fibrinolytic lysine binding sites and inhibits the fibrinolytic effect of fibrinolytic enzymes. On the other hand, it has anti-inflammatory effects. Plasmin activates and upregulates a cascade of inflammatory responses by activating pre-inflammatory cells and inducing pre-inflammatory gene expression [23]. TXA blocks this inflammatory activation by inhibiting the conversion of plasminogen to plasmin. Patients undergoing cardiopulmonary bypass and orthopedic joint replacement are generally treated with TXA to reduce systemic inflammation and blood loss [24].

TXA is widely used in surgical patients who need blood transfusion and hemostatic treatment. It can reduce the risk of bleeding and mortality in patients with TBI [5]. A large randomized controlled study (CRASH-2) involving 20,000 patients in 40 countries found that treatment with TXA within one hour after acute TBI reduced the risk of death from bleeding by 30%; Treatment with TXA 1 to 3 hours after trauma reduced the risk of death by 20%. Therefore, TXA may be a potential treatment for TBI patients. However, for TBI patients undergoing craniotomy for hematoma removal, there is still less evidence of the influence of TXA on their prognosis.

Safety is also our important consideration. TXA has been suggested to be at risk of cerebral thrombosis and secondary cerebral ischemia[25]. Cerebral ischemia is a secondary injury after TBI, which can aggravate neurological dysfunction and increase the mortality and disability[26, 27]. TXA may also increase intracranial pressure,

leading to intracranial hypo-perfusion [28, 29]. Thrombotic intravascular coagulation increased the incidence of intracerebral microthrombi [30]. However, a number of studies have shown that TXA is safe for TBI patients[6-8]. A multicentric, large-sample randomized controlled study (CRASH-3) found that TXA reduced the mortality of mild to moderate TBI patients without increasing the risk of thrombosis events(RR 0·98 (0·74-1·28), and there was no significant difference in the risk of epilepsy compared with the placebo group (1·09 [95% CI 0·90-1·33])[9]. Recently, a Meta-analysis reported that TXA probably does not increase the risk of adverse events [31].

To sum up, scientific and effective treatments for TBI patients are needed, and coagulation function is an important clinical indicator affecting the prognosis of TBI patients. In this study, we aim at investigating the effect and safety of perioperative intravenous administration of TXA in TBI patients undergoing craniotomy. We also want to explore the effect of TXA on the inflammatory response and the coagulation function of TBI patients, as well as its relationship with the prognosis. We are aimed at providing a basis for the perioperative TXA treatment for TBI patients and optimizing the perioperative treatment plan for TBI patients.

Summary

In summary, the study aims to investigate the effect and safety of TXA in TBI patients undergoing neurosurgery for hematoma removal. If the result of this study is positive, it will provide evidence for optimal perioperative treatment to improve the prognosis of TBI patients who need craniotomy.

Dissemination

The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Informed Consent

All participants in this trial will sign informed consent documents. Moreover, all participants will be given sufficient time to decide whether to participate in this study. The entrusted agent (relatives or legal representatives) of the patients who participate in the study will have the right to obtain all relevant information, and they will be allowed to withdraw their consent or discontinue participation without restrictions at any time during the study. The confidentiality of participant records will be protected.

Timeline

The study will take approximately 2 years to complete enrolment and outcome assessment. The trial was registered at chictr.org.cn on 10 January 2021 (identifier ChiCTR2100041911). The study was approved by the Institutional Review Board at Beijing Tian Tan Hospital, Capital Medical University on 5 January 2021 (reference number KY2020-136-03).

Audits

The data monitoring committee will conduct audits through regular interviews, letters

or telephone. The data monitoring committee reserves the right to audit the recruitment of patients at any time. The auditing process will be independent from the investigators.

Amendments to the protocol

Amendments to the protocol will only be made by academic committee and with the approval of the Medical Ethics Committee, Beijing Tiantan Hospital, Capital Medical University. All modifications will be recorded. Any modifications will be applied to all subsequent patients, and the registration record will be updated.

Contributors BW was involved in the conception and design, data collection and analysis, and manuscript writing. WC and YL were involved in the conception and design, data collection and analysis, and manuscript revision. YY, JW, HY and YC were involved in the conception and design, data collection, and manuscript revision. All authors have read and approved the final manuscript.

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Ethics approval All procedures in the trial will be conducted in accordance with the World Medical Association's "Helsinki Declaration (version 19 October 2013)". The study plan (protocol version 1.0) was approved by the Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University, China (KY 2020-136-03). This study protocol has been registered at chictr.org.cn (ChiCTR2100041911).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____1_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	__top of page __
Funding	4	Sources and types of financial, material, and other support	_____8_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1 and 8 __
	5b	Name and contact information for the trial sponsor	_____1_____
	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	_____8_____
	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)	_____7_____

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	1-2
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	1-2
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)	2
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	2
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)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3
	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)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
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	4
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)	7

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	4-5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

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	3
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	3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	

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	
	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	4

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	_____
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	_____5_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____5_____
	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)	_____
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	___7_____
	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	_____5_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____7_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____1,7,8_____
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)	_____8_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	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	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
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	
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	
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	7
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	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	4

*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.

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Effect of tranexamic acid on the prognosis of patients with traumatic brain injury undergoing craniotomy: study protocol for a randomized controlled trial

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Effect of tranexamic acid on the prognosis of patients with traumatic brain injury undergoing craniotomy: study protocol for a randomized controlled trial

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Abstract

Introduction Abnormal coagulation function aggravate the prognosis of patients with traumatic brain injury (TBI). It was reported that the anti-fibrinolytic drug tranexamic acid (TXA) could reduce intracranial hemorrhage and mortality in non-operative TBI patients. However, there is a lack of evaluation of TXA in TBI patients undergoing craniotomy.

Methods and analysis This is a single-centre randomized controlled, double-blind, parallel study aiming to investigate the effectiveness and safety of TXA in TBI patients during the perioperative period. Blood loss and transfusion, neurological function, adverse events, mortality, serum immune-inflammatory cytokines will be collected and analyzed.

Ethics and dissemination Ethical approval has been granted by the Medical Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University (reference number: KY 2020-136-03). The results of this study will be disseminated through presentations at scientific conferences and publication in peer-reviewed journals.

Trial registration number ChiCTR2100041911.

Strengths and limitation of this study

- This is a randomized controlled, double-blind, parallel study to test the hypothesis

that TXA could improve prognosis of TBI patients undergoing craniotomy.

- The study will provide evidence for optimizing perioperative treatment of TBI patients undergoing craniotomy.
- There are nearly five hundred cases of TBI patients that need neurosurgery every year at Beijing Tian Tan Hospital, Capital Medical University. It is feasible and reasonable to complete the trial in 3 years.
- The study may not be generalized to other populations since it is a single-centre trial.

Key words Traumatic brain injury; Traumatic coagulation disorder; Tranexamic acid; Systemic inflammatory response

Introduction

About 1.5 million people die each year from traumatic brain injury (TBI), which has become the leading cause of death and disability worldwide. Brain tissue injury and hemorrhage are the main clinical manifestations of TBI. Systemic inflammatory reaction and abnormal coagulation function after TBI can cause secondary brain injury and aggravate cerebral hemorrhage, which has extremely adverse effect on the prognosis.

In recent years, many studies[1-3] have shown that abnormal coagulation function is common in TBI patients and is one of the main causes of secondary brain injury. The incidence of coagulation dysfunction on admission is about 26% in TBI patients, and over 60% of them have severe TBI.[4] A prospective study found that TBI patients with abnormal coagulation function had a 4.7-fold increase in mortality and an increased risk of poor prognosis compared with those without abnormal coagulation function.[5] Some studies[2-4 6] have confirmed the interaction between abnormal coagulation function, hyperfibrinolysis and systemic inflammatory reactions.

Tranexamic Acid (TXA) have anti-fibrinolytic and anti-inflammatory effect. Studies have reported that early use of TXA can reduce blood loss and mortality in TBI patients with non-surgical treatment.[7 8] Some studies [6 9-12] suggested that the use of TXA could reduce the mortality and disability of the TBI patients and probably does not increase

the risk of adverse events. TXA may be a potential treatment for TBI patients.

It is generally believed that the abnormal coagulation function after TBI is closely related to the degree of brain tissue damage. de Oliveira Manoel et al. have shown that more than 60% of patients have severe TBI are accompanied by abnormal coagulation function.[4] The incidence of abnormal coagulation function is increased in TBI patients combined with systemic injury compared with simple TBI patients.[13]

Kearney et al have found that severe TBI patients have a higher mortality rate and a higher degree of abnormality in Glasgow Coma Scale (GCS), Simplified Acute Physiological Score (SAPS) and disseminated intravascular coagulation (DIC).[14] Urgent decompressive craniotomy is recommended for severe TBI patients with severe craniocerebral trauma, severe cerebral edema, epidural hematomas and subdural hematomas to reduce ICP and mortality and improve neurological clinical outcomes.[15] [16] For severe TBI patients complicated by acute traumatic coagulopathy and severe systemic inflammatory response, promptly correction of coagulopathies and anti-inflammatory treatment should take into consideration.[16] [17] It is not clear whether the use of TXA can improve the prognosis of TBI patients requiring emergency craniotomy. It still needs further research to determine the effect of TXA on the systemic inflammatory reaction and coagulation function in TBI patients undergoing craniotomy procedures.

To sum up, this study intends to evaluate the efficacy and safety of intravenous administration of TXA in TBI patients undergoing craniotomy procedures. We also aim to explore the impact of TXA on systemic inflammatory response, coagulation function, the relationship between these effects and prognosis. This study will provide the basis for further development of perioperative TXA usage and optimize perioperative treatment plan for TBI patients.

Hypothesis to be tested

In TBI patients undergoing craniotomy, intravenous administration of TXA improves the patient clinical outcome, alleviates systemic inflammatory response and coagulation dysfunction.

Specific objectives

Primary objectives

Measure whether intravenous administration of TXA improves the GOSE outcome in TBI patients undergoing craniotomy procedures at discharge.

Secondary objectives

The secondary objectives of this study include the following aspects:

1. Bleeding: measure whether intravenous administration of TXA for TBI patients undergoing craniotomy procedures could reduce the intraoperative blood loss and blood transfusion.
2. Safety: observe whether intravenous administration of TXA could increase thrombotic events and postoperative infections for TBI patients undergoing craniotomy.
3. Clinical outcome: investigate whether perioperatively administration of TXA could improve the Coma Recovery Scale - Revised (CRS-R) at discharge, reduce the in-hospital and 30-day mortality rate of TBI patients undergoing craniotomy.

Exploratory objectives

We will do explored laboratory tests to examine whether TXA could reduce the level of plasma traumatic stress factors, inflammation biomarkers and the abnormalities of coagulation indicators.

Methods and analysis

Study design and setting

This study is a single-centre randomized double-blind placebo-controlled parallel study to explore the effect of intravenous administration of TXA on the clinical outcome of TBI patients undergoing craniotomy. From February 2021 to November 2023, TBI patients undergoing emergency craniotomy will be recruited from Beijing Tian Tan Hospital, Capital Medical University. Data will be collected consecutively from patients after written informed consent is obtained.

Inclusion (Eligibility) criteria

1. 18 to 65-year-old TBI patients scheduled for a craniotomy hematoma removal surgery.
2. availability of informed consent.

Exclusion criteria

1. allergic history to TXA;
2. taking thrombin;
3. taking anticoagulants;
4. history of chronic coagulation disorder;
5. history of thrombosis (deep vein thrombosis, pulmonary embolism, cerebral thrombosis, myocardial infarction, thrombophlebitis);
6. history of renal insufficiency;
7. pregnancy;
8. history of epilepsy;
9. with mental illness.

Intervention

The TXA group will be given TXA 2g (40ml). After the patient is routinely monitored in the operating room and the peripheral vein is established, injections will be pumped at the rate of 80ml/hour for 15min (loading dose, 20 mL 1g), and then 2.5ml/hour until the injection is completed (maintenance dose, 20mL, 1g for 8h).

Placebo

The placebo group will be received an equal volume of normal saline delivered at the same rate as TXA group.

Recruitment procedure and informed consent

Throughout the study period, a professional full-time quality control staff is in charge of contacting with the emergency department. When TBI patients arrive at the hospital, this staff will screen the patients for eligibility. All participants in this trial will sign informed consent documents. A detailed information regarding the study will be provided focusing on the duration, collection of blood samples and the follow-up plan.

The consent forms will be filled up by the anesthesiologist who is in charge of the anesthesia. A copy of the consent form along with the information sheets will be provided to each participant. In the consent form, there is a separate provision for consent of biological samples where the participants may agree or refuse. TBI patients undergoing neurosurgery are always unconsciousness. Therefore, the entrusted legal representative of the participants has the right to obtain all relevant information and sign the consent. They will be given sufficient time to decide whether to participate in this study. In case of illiterate representatives, we will obtain thumbprints after getting signature from an impartial witness who is not part of research team. They will be allowed to withdraw their consent or discontinue participation without restrictions at any time during the study. The confidentiality of participant records will be protected.

Allocation and randomization

After meeting the eligibility criteria and signing the informed consent to participate in the study, 1288 patients will be randomly allocated in a 1:1 ratio into one of two groups: (1) TXA group and (2) Placebo group. Each patient is assigned a packet according to his/her ID number which is sequentially numbered. This packet is only labelled with general study information and the unique ID number. The list that links the ID number to the randomization code is kept with the statistician who generated it using Stata software version 15.1. The statistician is otherwise not involved in the study.

Blinding

After the informed consent form is signed and the patient enters the operating room, the full-time quality control staff not involved in clinical treatment will prepare TXA/Placebo syringes according to the randomization code for the patients.

Patients/representatives, anesthesiologists, and investigators who are responsible for enrolling and observing the primary and secondary outcomes will be concealed throughout the study. Blinding will be discontinued after all data collection is completed. Furthermore, serious life-threatening adverse events leading to prolonged hospital stay or death will be reported to the principal investigator (PI), and the blinding

will be broken following consultation with the PI if necessary.

Timeline

The trial was registered at chictr.org.cn on 10 January 2021 (identifier ChiCTR2100041911). The study was approved by the Institutional Review Board at Beijing Tian Tan Hospital, Capital Medical University on 5 January 2021 (reference number KY2020-136-03). The first participant in the study was enrolled in February 2021 and we plan to enroll for 3 years. End of follow-up of patients will be completed approximately 30 days after the last enrollment.

Anesthesia management

Standardized procedures will be applied.[15 18 19] After the patient enters the operating room (room temperature is 24 ℃ ~ 26 ℃), standard routine monitoring will be applied, including non-invasive blood pressure, electrocardiography, pulse oxygen saturation, end-tidal carbon dioxide partial pressure, and body temperature. The experimental medicines will be administrated intravenously. Induction drugs will include sufentanil (0.3 ~ 0.4 mg/kg), etomidate (0.3~ 0.4 mg/kg), and rocuronium (0.6 mg/kg). After induction, endotracheal intubation will be followed, and the respiratory parameters will be adjusted to maintain $P_{ET}CO_2$ within physiological range (35~45 cmH_2O). Arterial and central venous catheterization will be established. Intraoperative anesthesia will be adjusted with propofol (2~6 mg/kg/hour), remifentanil (0.1~0.2 mg/kg/min) and sevoflurane (0.5~1%) to maintain the MAP ≥ 60mmHg, and muscle relaxants will be added when necessary. After the operation, the tracheal catheter will be kept or removed (according to circumstances of patients) and patients will be transferred to the intensive care unit (ICU) or neurosurgical ward.

Laboratory procedures

3mL of blood will be collected from the patients before anesthesia, 1 day and 7 days after surgery. Blood will be centrifuged at 3,000 rotations for 10 minutes, and the supernatant will be collected and stored at -80 °C.

The blood sample will be analyzed for the following:

1. Traumatic stress factors: Adcorticotropic hormone (ACTH), adrenaline (AD), Norepinephrine (NE), cortisol, lactic acid.
2. Immune inflammatory factors: Human monocyte chemotactic protein-1 (McP-1), tumor necrosis factor-α (TNF-α), C reactive protein (CRP), peripheral blood leukocyte count and classification, interleukin-1 (IL-1), IL-6, and IL-10.

Follow-up

Clinical prognosis of postoperative outcomes will be collected through telephone or interview 30 days after admission date. These will include neurological recovery, re-operation, major postoperative complications, death, etc.

Outcomes

Primary outcome

The primary outcome is the Glasgow Outcome Scale - extended (GOSE) [20] at discharge. The GOSE is the most highly cited outcome scale in studies of TBI. In a review of outcome measures, Nichol and colleagues listed five features of the ideal outcome scale for head injury: it should be logistically simple, reliable, valid, stable and free to administer[21]. The GOSE meet all of these criteria, and is widely recommended as the main outcome measure in studies of TBI.[22-24] GOSE includes 8 categories: Dead (1), Vegetative State (2), Lower Severe Disability (3), Upper Severe Disability (4), Lower Moderate Disability (5), Upper Moderate Disability (6), Lower Good Recovery (7), and Upper Good Recovery (8). GOSE 1~4 is defined as unfavorable outcome, GOSE 5~8 is defined as favorable outcome.

At the day of the discharge, the specially trained staff will go to the ward or ICU to do the evaluation of GOSE. The discharge time will be determined by the neurosurgeon. A TBI patient will be allowed to discharge when meeting the following conditions: ① intracranial hematoma is in stable absorption phase; ② intracranial pressure (ICP) is stable, no more dehydration treatment is needed; ③ no more surgical treatment is

needed; ④ severe complications are controlled well; ⑤ incision is dry without infection and effusion.

Secondary outcome

1. Intraoperative blood loss: the intraoperative blood loss will be calculated based on the previous study.[25] The blood loss via the suction will be determined by subtracting the added fluids (heparin and saline solutions) from the total volume contained in the surgical canister. The cotton slivers and pieces used during operation will also be calculated at the end of the surgery. A soaked sliver equals 5 mL blood. A soaked pieces equals 1 mL blood.
2. Blood transfusion: we will record the blood transfusion volume during operation and postoperatively in ICU and ward, including red blood cells, fresh frozen plasma, fibrinogen and platelets.
3. Thrombotic events: we will observe the incidence of thrombotic events during hospitalization, including myocardial infarction, pulmonary embolism, deep vein thrombosis, and cerebral infarction.
4. Infections: we will record the incidence of postoperative infection complications, including pneumonia, incision infection, intracranial infection, and urinary system infection.
5. Coma Recovery Scale - Revised (CRS-R):[26] the specially trained staff will estimate the CRS-R of all the participants at the day of discharge. We will choose a cut-off score of 8 in our assessment because of the best odds avoiding false positive and negative errors in our analysis.[27]
6. 30-day mortality rate after surgery.
7. In-hospital mortality rate.

Exploratory outcomes

1. Hospitalization length and costs: we will record the days of hospitalization after surgery. This will be calculated from the second day after surgery to the discharge day. The hospitalization costs include the total cost, drug costs, examination and laboratory costs and nursing costs. These will be analyzed separately.
2. Traumatic stress and systemic inflammatory response: to evaluate the effect of TXA

on traumatic stress and systemic inflammatory response, we will examine the following plasma biomarkers: ACTH, AD, NE, cortisol, lactic acid, McP-1, TNF-α, CRP, peripheral blood leukocyte count and classification, IL-1, IL-6, and IL-10.

3. Coagulation functions: the coagulation function and thromboela-stogram (TEG) will be examined before surgery, 1 day and 7 days after surgery. The coagulation function test includes the following indicators: thrombin time (TT), fibrinogen (Fbg), activated partial thromboplastin time (APTT), international standardized ratio (INR), prothrombin time (PT), fibrin degradation products (FDP).

Safety considerations, safety monitoring and adverse events (AEs) reporting

All AEs and serious adverse events (SAEs) will be recorded by the study staff. All immediate AEs intervention will be documented for all participants. All AEs and SAEs will be followed up until resolution or stabilization as judged by anesthesiologist or neurosurgeon and the principal investigator (PI). All SAEs will be followed up until satisfactory resolution or until the treating physicians and the PI deem the event to be chronic or the participant to be stable.

SAEs, which include critical or life-threatening complications or death, will be documented from the time of enrolment throughout the study period. All SAEs and AEs will be reported to the Ethics Committees and the Data and Safety Monitoring Board (DSMB) of the study within 24 hours of awareness of the event.

Data and Safety Monitoring Boards

The DSMB comprises an anesthesiologist, neurosurgeon, and statistician. The DSMB is independent from the sponsor and has no competing interest. The DSMB members will decide the study stopping rules, review the AEs and SAEs reported in the study. They will determine the severity, cause, and consequences. Any important protocol modification will be thoroughly communicated with the DSMB members and will obtain amendment clearance from the institutional review board (IRB). We do not have a plan to perform interim analyses. Therefore, we do not have stopping guidelines based on the results of interim analyses.

Sample size calculations

The reported unfavorable clinical outcome rate in severe TBI patients is 42%-59%.[28-30] Our data showed that 54% of TBI patients undergoing craniotomy for hematoma evacuation had unfavorable outcome. Thus, we suppose the unfavorable clinical outcome rate in the placebo group is 54%, and the anticipated unfavorable clinical outcome rate in the TXA group reduce by 15% (54% to 46%). The sample size was calculated with the model of Test for Two Proportions [Differences] in PASS V.11 software (NCSS, LLC, USA). Given an alpha level of 0.05, a beta level of 0.2, the total sample size required is 613 in each group. Considering a 5% rate of loss to follow-up, it would be necessary to include 644 participants per group (total: 1288 participants). There are approximately 40 TBI patients undergoing craniotomy in Beijing Tian Tan hospital every month. Such a sample size could be achieved in our study.

Data collection and management

Investigators will explain the benefits of participating in the trial to patients and/or their authorized representative before surgery. Outcome investigators will receive training on all outcome measures. The anesthesiologist in charge will record the patients' intraoperative data, including blood pressure, heart rate, oxygen saturation, blood loss, urine volume, medicine, infusion volume, transfusion volume and operation time, et al. The data managers will use double data entry to enter data into the EpiData database. An inspector will examine the data, create records, and revise these records as necessary. Each participant will have a unique study identifier, and their data will be recorded by an independent data manager. The data will be electronically stored in the EpiData database and undisclosed to other researchers until the study is completed. The final dataset will be handed over to statistical analysts for statistical analysis. Regular data checks and double data entry will be applied to promote data quality.

Record retention and archival

All the study documents will be archived by the study sites and retained for three years

after the completion of the study.

Statistical analysis

Statistical analyses will be performed using STATA V.15.1 statistical software (Statacorp LLC, USA). All measured data will be reported as the mean ± standard deviation (x ± s), interquartile range (IQR, 25 - 75% percentile), or number (%).

For the primary outcome, GOSE 1~4 will be defined as unfavorable outcome, GOSE 5~8 will be defined as favorable outcome. Chi-square test will be used to evaluate the primary outcome. For the secondary outcomes, we will use t test or rank sum test to analyze intraoperative blood loss, blood transfusion volume and CRS-R. Chi-square test or Fisher's exact test will be used to analyze the thrombotic events rate and infection rate after surgery. Chi-square test or univariate logistic regression analysis will be used for in-hospital and 30-day mortality rate after surgery. And for the length of hospitalization and hospitalization costs, we will use rank sum test. Subgroup analysis will be performed based on age, sex, GCS, time from injury to intervention. Interaction analysis might be involved to evaluate the differences between TXA group and placebo group in different subgroups.

All randomized participants with informed consent will be analyzed. If unintended missing data related to the primary outcome account for more than 5%, this will be handled with multiple imputation. Analyses will be performed according to the intention-to-treat principle.

Patient and public involvement

Patients and the public will not be involved in the development of the research or the design of the study. Study results will be disseminated by publication in a medical journal and poster presentation at a medical conference.

Discussion

This study is a single-centre randomized double-blind placebo-controlled parallel study. To evaluate the influence of perioperative intravenous TXA treatment on the

prognosis of TBI patients undergoing craniotomy for hematoma removal after emergency admission to Beijing Tian Tan Hospital. We also want to explore the influence of TXA on perioperative coagulation function and systemic inflammatory response of patients and its relationship with prognosis.

The World Health Organization has declared TBI to be the leading cause of death and disability worldwide by 2020.[31] Cerebral hemorrhage is the main clinical manifestation of TBI, and traumatic coagulation disorder is the main cause of progressive aggravation of cerebral hemorrhage. Studies have reported that the incidence of abnormal coagulation function after TBI is 35.2 % (29.0 %~41.4 %), and the mortality rate of patients with simple TBI complicated with abnormal coagulation function is 17~86 %.[32] Compared with TBI patients without coagulation dysfunction, the mortality rate of TBI patients with coagulation dysfunction is 4.7 times higher, and the risk of poor prognosis is also increased.[5] The abnormal coagulation function after TBI is directly related to the degree of brain tissue damage.[14] In addition, systemic inflammatory response after TBI can aggravate coagulation dysfunction in TBI patients, which is one of the important causes of secondary brain injury.[33]

Studies suggest that the main mechanism leading to abnormal coagulation function after TBI is the activation of tissue plasminogen, hyperfibrinolysis, and disruption of the balance between coagulation and bleeding.[34] After severe TBI, a strong stress response occurs, which then induces systemic inflammatory response syndrome, leading to increased bleeding, increased blood transfusion, systemic organ failure, aggravating patients' abnormal coagulation function, and resulting in increased mortality.[35 36] In addition, excessive consumption of coagulation factors and platelet dysfunction,[37] hypoperfusion and protein-C pathway activation, hypothermia, metabolic acidosis, and hemodilution can also lead to coagulation dysfunction after TBI.[38] In TBI patients, the blood-brain barrier is destroyed, fibrinogen and its degradation products enter the brain, activate the inflammatory reaction cascade and the immune response in the brain, leading to lymphocyte infiltration, glial cell activation, cytokine release and reactive oxygen element production in the brain. These lead to axonal demyelination and neuronal damage.[39] Therefore, abnormal coagulation function

significantly increases the mortality of patients, the regulation of patients' coagulation function has great clinical significance for improving the prognosis of patients, which has attracted more and more attention.

TXA is an anti-fibrinolytic drug that competitively binds to the fibrinolytic lysine binding sites and inhibits the fibrinolytic effect of fibrinolytic enzymes. On the other hand, it has anti-inflammatory effects. Plasmin activates and upregulates a cascade of inflammatory responses by activating pre-inflammatory cells and inducing pre-inflammatory gene expression.[40] TXA blocks this inflammatory activation by inhibiting the conversion of plasminogen to plasmin. Patients undergoing cardiopulmonary bypass and orthopedic joint replacement are generally treated with TXA to reduce systemic inflammation and blood loss.[41]

TXA is widely used in surgical patients who need blood transfusion and hemostatic treatment. It can reduce the risk of bleeding and mortality in patients with TBI.[9] A large randomized controlled study (CRASH-2) involving 20,000 patients in 40 countries found that treatment with TXA within one hour after acute TBI reduced the risk of death from bleeding by 30%; Treatment with TXA 1 to 3 hours after trauma reduced the risk of death by 20%. Therefore, TXA may be a potential treatment for TBI patients. However, for TBI patients undergoing craniotomy for hematoma removal, there is still less evidence of the influence of TXA on their prognosis.

Safety is also our important consideration. TXA has been suggested to be at risk of cerebral thrombosis and secondary cerebral ischemia.[42] Cerebral ischemia is a secondary injury after TBI, which can aggravate neurological dysfunction and increase the mortality and disability.[43 44] TXA may also increase intracranial pressure, leading to intracranial hypo-perfusion.[45 46] Thrombotic intravascular coagulation increased the incidence of intracerebral microthrombi.[47] However, a number of studies have shown that TXA is safe for TBI patients.[6 10 11] A multicentric, large-sample randomized controlled study (CRASH-3) found that TXA reduced the mortality of mild to moderate TBI patients without increasing the risk of thrombosis events(RR 0·98 (0·74-1·28), and there was no significant difference in the risk of epilepsy compared with the placebo group (1·09 [95% CI 0·90-1·33]).[12] Recently, a Meta-analysis reported that TXA

probably does not increase the risk of adverse events.[48]

To sum up, scientific and effective treatments for TBI patients are needed, and coagulation function is an important clinical indicator affecting the prognosis of TBI patients. In this study, we aim at investigating the effect and safety of perioperative intravenous administration of TXA in TBI patients undergoing craniotomy. We also want to explore the effect of TXA on the inflammatory response and the coagulation function of TBI patients, as well as its relationship with the prognosis. We are aimed at providing a basis for the perioperative TXA treatment for TBI patients and optimizing the perioperative treatment plan for TBI patients.

Summary

In summary, the study aims to investigate the effect and safety of TXA in TBI patients undergoing neurosurgery for hematoma removal. If the result of this study is positive, it will provide evidence for optimal perioperative treatment to improve the prognosis of TBI patients who need craniotomy.

Dissemination

The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

Audits

The data monitoring committee will conduct audits through regular interviews, letters or telephone. The data monitoring committee reserves the right to audit the recruitment of patients at any time. The auditing process will be independent from the investigators.

Amendments to the protocol

Any deviations from the protocol will be fully documented in a report form, reported to all regulatory bodies, and thoroughly recorded in a protocol deviation log. The DSMB and PI will determine the protocol amendments. Protocol amendments will be sent as updated protocols to investigators. A copy of each revised protocol will be added

to the Investigator Site File. The protocol will also be updated in the clinical trials registry website.

Contributors BW was involved in the conception and design, data collection and analysis, and manuscript writing. WC and YL were involved in the conception and design, data collection and analysis, and manuscript revision. YY, JW, HY and YC were involved in the conception and design, data collection, and manuscript revision. All authors have read and approved the final manuscript.

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Ethics approval All procedures in the trial will be conducted in accordance with the World Medical Association's "Helsinki Declaration (version 19 October 2013)". The study plan (protocol version 1.0) was approved by the Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University, China (KY 2020-136-03). This study protocol has been registered at chictr.org.cn (ChiCTR2100041911).

Strategies to improve the adherence to protocols

The anesthesiologist who implements anesthesia in this study will be trained to obey the standardized procedure. The investigator staff will be well trained to perform preoperative recruitment, assessment and postoperative follow-up. We will train the whole study team to standardly use the assessment scales involves in this study. And the investigator who will do the assessments will be blind to the intervention.

Competing Interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1,7,17
Protocol version	3	Date and version identifier	top of pages
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,16
	5b	Name and contact information for the trial sponsor	not applicable
	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	not applicable
	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)	10,11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-3
	6b	Explanation for choice of comparators	not applicable
Objectives	7	Specific objectives or hypotheses	3-4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4-5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	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)	not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	not applicable
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	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	11-12
	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	17

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	11-12
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	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	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)	12-13
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	10-11
	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	11
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	10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1,10,16,17
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5-6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
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	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	17
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	not applicable
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	15-16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental for editors only
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	8

*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.