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Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) Trial: Study Protocol for a Randomized Placebo-controlled Trial

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Abstract

Background: The neuroprotective medication, butylphthalide (NBP), has been proved to protect against cerebral ischemic injury. Evidence about whether NBP influence the outcomes of patients with acute ischemic stroke receiving revascularization treatment is limited. This study aims to evaluate whether the additional NBP therapy could promote the recovery of neurological deficits of patients receiving the standard intravenous recombinant tissue plasminogen activator (rt-PA) and endovascular treatment.

Methods and analysis: This study is designed as a randomized, double-blind, placebo-controlled, multiple-center parallel group trial. The endovascular treatment includes intraarterial thrombolysis and mechanical thrombectomy. The sample size is estimated at 1200 patients. Eligible patients will be randomized in a 1:1 ratio to receive either NBP or placebo daily for 90 days, which include 14 days of injection and 76 days of capsules. The first use of NBP/placebo was started within 6h from onset of the ischemic stroke. The primary outcome is the recovery of functional outcome assessed by the 90-day modified Rankin Scale adjusted for baseline the National Institutes of Health Stroke Scale (NIHSS). The primary safety outcome is the percentage of serious adverse events within 90 days. BAST will determine whether the application of NBP can add benefit to patients with acute ischemic stroke receiving intravenous thrombolysis or endovascular Treatment.

Ethics and dissemination: The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02.

Trial registration: NCT03539445; Registered July 17, 2018, https://www.clinicaltrials.gov/ct2/show/NCT03539445?term=NCT03539445&draw=2&rank=1

Keywords: Butylphthalide; Acute Ischemic Stroke; Intravenous Thrombolysis; Endovascular Treatment

Strengths and limitations of this study

- This study is that the NBP/placebo requires application within 6h from onset of the ischemic stroke. Treatment with intravenous rt-PA is conducted within 4.5h, and endovascular treatment is within 6h.

- The sample size was estimated at 1200 patients. It seems rather small, especially for a phaseⅣ intervention trail.

- Strict enrolling criteria including the first injection starting with 6h from onset seems a challenge in patient selection, which may result in a bias between primary stroke centers and comprehensive stroke centers.

- The BAST study is conducted in China only, and the results are limited to generalize to other ethic population.

Background

Ischemic stroke has high prevalence, recurrence, morbidity and mortality, which has arisen to the third leading causes of death over the world[1 2]. With the application of intravenous recombinant tissue plasminogen activator (rt-PA) and endovascular treatment, many patients have obtained a standard therapy in the acute phage. However, a large proportion of neurological deficits were not significantly improved, even for the patients who received intravenous rt-PA and endovascular treatment[3-11]. Due to this condition, some neuroprotective medicine have received the clinicians' attention, which aimed to reduce the neuronal damage and improve the neurological deficits. For instance, the ESCAPE-NA-1 study found that nerinetide had a treatment effect among patients who were not treated with intravenous thrombolysis, although this finding required confirmation, it suggested that neuroprotection in human stroke might be possible[12].

Butylphthalide (NBP), a well-known neuroprotective medication, is a family of compounds initially isolated from the seeds of Apium graveolens Linn, of which active ingredient is dl-3-N-butylphthalide. NBP was reported to have effects in reducing the cerebral ischemic damage and improving patients' clinical outcomes. The potential mechanisms were confirmed in experimentation on animals, which included promoting microcirculation[13], protecting blood brain barrier[14], and releasing oxidative stress[15], mitochondrial dysfunction[16], post stroke inflammation[17], and cerebral edema[18]. NBP has been approved for use in patients with ischemic stroke in China since 2002. With the evolution of reperfusion treatment in acute ischemic stroke recently, it is still undefined

whether combination therapy with NBP could improve the outcomes in those patients.

This article describes the rational and design of the Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) trial, aiming to investigate whether BNP is an effective and safe medication for the patients who received intravenous rt-PA and endovascular treatment.

Methods/design

Study Design

The BAST trial is a randomized, double-blind, placebo-controlled, multiple-center parallel group study. It aimed to assessing the efficacy and safety of NBP in patients who received intravenous rt-PA, and/or endovascular treatment. The participants will be recruited from the departments of neurology or interventional neuroradiology at about 30 hospitals across China. The eligible patients will be randomized in a 1:1 ratio to receive either NBP or placebo daily for 90 days. They will be visited at randomization, 2 days after the first injection, day 14, day 30, day 60 and day 90 (Table 1). The BAST design is in compliance with the Declaration of Helsinki. All patients in this trail will be required to sign an informed consent form. The BAST study has been approved by the ethics committees of all participating hospitals. It was registered in ClinicalTrial.gov (NCT03539445).

Objective

The primary objective of the trial is to determine whether the application of NBP could improve functional outcome of acute ischemic stroke patients receiving intravenous thrombolysis or endovascular treatment.

Participants

Patients will be enrolled if they meet the inclusion and exclusion criteria summarized in Table 2. Actually, researchers took continuous selections on patients who arrived at hospital with the complaint of sudden neurologic function deficits. Then those patients would be assessed to figure out whether they meet the inclusion and exclusion criteria standard of the BAST trial. The investigators fully inform the patient of the uncertainty of the randomized controlled trial, the equal opportunity to use the test medication or placebo, the prognosis of the disease, and the adverse reactions that can occur, which are ultimately weighed by the patient or relatives. Patients or his/ her legal representative will sign a consent form prior to enrollment.

Randomization

The randomization procedure is based on a computer-generated code and permuted blocks. This allows the eligible patients to be assigned NBP or placebo in a 1:1 ratio. According to the enrollment time, patients will be assigned a serial random number and provided with corresponding medicine which are beforehand blind-covered. Both the researchers and patients are blind to the medicine.

Procedures

Except for intravenous rt-PA and/or endovascular treatment eligible, patients included will receive adjunctive therapy with NBP/placebo. Patients of experimental group will receive NBP and sodium chloride injection 100ml twice/day in the initial 14 days, and then take NBP soft capsules 0.2g triple/day for the rest 15th to 90th day; controlled group will receive NBP placebo injection 100ml twice/day in the initial 14 days and then take NBP placebo soft capsules 0.2g triple/day for the rest 15th to 90th day. The first use of NBP/placebo injection should be started within 6h from onset of the ischemic stroke. The injections are recommended to use for 14 days, and at least 10 days. The capsules should be used on the second day after the injection treatment ends, and are recommended to use until day 90. Every injection treatment should last for at least 50 minutes, and 6h apart. Patients should take capsules daily before meals, and make medicine administration record for researchers to check. The steering committee will make recommendations for concomitant medication. Specially, uriklin, edaravone and any ginkgo-containing injections are all prohibited in this study.

Outcomes

Primary outcome

The primary efficacy outcome is the proportion of patients with a favorable outcome at 90 days after randomization. A favorable outcome[12 13] was defined as a modified Rankin Scale score of 0 in patients with a baseline the National Institutes of Health Stroke Scale (NIHSS) score of 3 to 7, a modified Rankin Scale score (mRS) of 0 to 1 in patients with a baseline NIHSS score of 8 to 14, and a mRS of 0 to 2 in patients with a baseline NIHSS score of 15 to 22.

Secondary outcomes

The secondary efficacy outcomes include: The difference value of the NIHSS between Day 14/Day 90 and the baseline; the cerebral infarction volume at day 14; the recanalization rate during the first 24 hours; the percentage of symptomatic intracranial hemorrhage (defined by ECASS III trail) during the first 24 hours; recurrent symptomatic ischemic stroke and vascular events within 90 days; any vascular complications with vascular events (recurrent symptomatic ischemic stroke, myocardiac infarction, vascular death) at day 90; the life quality score estimated by EuroQol 5D at day 90; the cognitive function estimated by Mini-mental State Examination and Montreal Cognitive Assessment Scales at day 90; functional outcome (A modified Rankin Scale score of 0 in patients with a baseline NIHSS core of 4 to 7, a modified Rankin Scale score of 0 to 1 in patients with a baseline NIHSS score of 8 to 14, and a modified Rankin Scale score of 0 to 2 in patients with a baseline NIHSS score of 15 to 25) at day 14; the difference value of the NIHSS between Day 14/Day 90 and the baseline.

Safety outcomes

The primary safety outcome is the percentage of serious adverse events within 90 days, which includes any events resulting in prolonging-hospital time, permanent damage to the system/organ, life-threatening or death. The secondary outcomes include: symptomatic intracranial hemorrhage within 90 days; total mortality within 14 days and 90 days; adverse events within 14 days and 90 days; serious adverse events within 14 days;

Power and Sample Size Calculation

According to previous study[14], we assumed that the proportion of patients with functional outcome (based on the adjusted mRS) is 50%, proportion of patients with functional outcome in the experimental group is 60%.The test level is set as 0.05. Giving the test power of 90% and the significance level of 5% (two sided), each group requires 550 patients. Considering 10% of lost visits, 600 patients are required for each group, and 1200 patients are required for this study.

Statistical Analyses

The primary analysis will be based on the intention to treat principle. Primary efficacy of the two groups will be compared by Chi-square test, and logistic regression will be used to calculate the odds ratio and 95% confidence interval. Missing outcome data will be imputed using the last observation carried forward (LOCF) method. The significance level will be set at 0.05 and all statistical tests will be two tailed. In addition, after 1/2 and 3/4 of participants completed, formal interim analyses of the primary outcome will be conducted to consider stopping the trial for overwhelming efficacy or for futility. Overwhelming efficacy is estimated using O'Brien–Fleming boundaries on the binary outcome of 90-day favorable outcome, corresponding significance levels are 0.003, 0.018 and 0.044.

Ethical dissemination

The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02.

Discussion

The BAST trial is a randomized control study, in phase Ⅳ. It was carried out in Chinese population. This trial explores the efficacy and safety of BNP, a typical neuroprotective medication, for patients with acute ischemic stroke receiving intravenous rt-PA and endovascular treatment.

Several reports[14-18] indicated that NBP may have a beneficial effect on patients with ischemic stroke. A multi-center, randomized, double-blind and placebo-control study showed that the NBP treatment group had a significant higher national rating scale score than the control group, and two groups had no significant deference in the rate of adverse events[19]. A systematic review reported that involved 21 randomized controlled trials reported NBP could improve the neurological function after acute ischemic stroke and appeared to be safe[20]. Another systematic review that involved 12 randomized controlled trials reported the combination use of NBP and standard anti-ischemic stroke drugs was more effective than standard drugs[21]. In this study, we will further explore the efficacy and safety of BNP in patients receiving intravenous rt-PA and endovascular treatment.

In vitro experiment has demonstrated that NBP can protect endothelial cells against oxidative/nitrosative stress and subsequent cell death, by enhancing the expression of hypoxia inducible factor-1 alpha[22]. The protective effect on mitochondrial function was

proved in early animal studies, which demonstrated that NBP improved the activities of Na^+/K^+-ATPase and Ca_2^+-ATPase in mitochondria[23]. NBP was also found to prevent the occurrence of ischemic stroke via the improvement of cerebral microvessels in stroke-prone renovascular hypertensive rats[24]. NBP administration ameliorated the reperfusion-induced brain damage via enhancement of hepatocyte growth factor and inhibition to TLR4/NF-kB and the pro-inflammatory cytokines in vivo and in vitro[25]. Additionally, many recent studies showed that treatment of NBP could influence the level of proteins in execution-phase of cell apoptosis, such as caspase-3 and caspase-9[23]. This influence could be potential approach to prevention of further cellular death in the ischemic penumbra. Above all, BNP protects against ischemic cerebra injury through several mechanisms, including alleviating oxidative damage, regulating mitochondrial dysfunction, improving microcirculation, inhibition of apoptosis and inflammatory response. These effects by NBP constitute the theoretical basis of this study. Based on this, we speculate that NBP might display a role in resisting ischemia reperfusion injury after intravenous rt-PA and endovascular treatment, and the combination therapy might improve patients' recovery of functional outcome.

One strength of this study is that the NBP/placebo requires application within 6h from onset of the ischemic stroke. Treatment with intravenous rt-PA is conducted within 4.5h, and endovascular treatment is within 6h. This suggests that the neuroprotective treatment is synchronised with recanalization treatment in this trail. As we know, almost immediately after vascular occlusion, the ischemic cerebra injury starts. The reperfusion injury after recanalization may aggravate the tissue damage sometimes. Different from

most of the previous studies[21], in which neuroprotective medicine was used in 48h, this study makes neuroprotective medicine used in the superacute ischemic injury phase. We wanted to demonstrate whether patients receiving this combination therapy in this phase could achieve a better functional outcome.

This study has some limitations. The sample size was estimated at 1200 patients. It seems rather small, especially for a phaseⅣ intervention trail. However, this conservative estimate allows us to estimate the primary outcome parameter with sufficient precision. Strict enrolling criteria including the first injection starting with 6h from onset seems a challenge in patient selection, which may result in a bias between primary stroke centers and comprehensive stroke centers. Finally, the BAST study is conducted in China only, and the results are limited to generalize to other ethic population.

List of abbreviations

BAST, Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment; LOCF, last observation carried forward; mRS, modified Rankin Scale score; NBP, butylphthalide; NIHSS, the National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.

Authors' contributions

All authors participated in the conception and design of the study. All authors are responsible for the patients' enrolment and data acquisition in their institution. All

authors approved the final manuscript version, and accounted for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work were appropriately investigated and resolved. All authors have read and approved the manuscript.

Funding statement

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Competing interests statement

The authors declare that they have no competing interests.

Trial Status

The current protocol version 21.0, 12 December 2019. This trial is in the process of recruiting participants. The actual trial enrolment started on 17 July 2018. We expect to enroll the target sample size by September 2022 and plan to continue with follow-up until December 2022.

Consent for publication

Not applicable.

Availability of data and material

The data generated from this study will be made available on reasonable request and approval by the corresponding author.

Acknowledgements

None.

Data and safety monitoring board

The data safety and monitoring board will monitor the progress of the study to ensure the patient safety and the highest standards of ethics. Annual monitoring will be performed by an independent clinical monitor. Interim progress reports will be sent to the academic committee.

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Table 1. The visit plan.

Measures	Baseline	Day 2	Day 14	Day 30	Day 60	Day 90
Demographics	×					
History of present illness	×					
mRS	×	×	×	×	×	×
Previous history	×					
Medication	×		×	×	×	×
NIHSS	×	×	×			×
Head CT	×					
Head MRI	×		×			
ASPECT	×					
Lab examination	×		×			
Electrocardiograph	×					
Inclusion & exclusion criteria	×					
Informed consent	×					
randomization	×					
Injection	×					
Compliance			×	×	×	×
Special lab test		×	×			×
TOAST classification			×			
OCSP classification	×					
EQ-5D				×	×	×
MMSE			×			×

MoCA			×			×
Soft capsules			×			
AE/SAE		×	×	×	×	×

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECT: Alberta Stroke Program Early CT Score; TOAST: Trial of Org 10 172 in acute Stroke Treatment; OCSP: Oxfordshire Community Stroke Programme; EQ-5D: EuroQol 5D; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; AE/SAE: Adverse Event /Serious Adverse Event .

Table 2. Inclusion and exclusion criteria for the BAST study

Inclusion Criteria
• age years
• diagnosed with acute ischemic stroke
• within 6 hours from symptom onset
• baseline NIHSS score ranging 4 from 25
• receiving intravenous rt-PA, or endovascular treatment (including intraarterial thrombolysis and mechanical thrombectomy), or intravenous rt-PA bridging endovascular treatment
• signing informed consent
Exclusion Criteria
• Modified Rankin Scale.mRS/>1 at randomization (pre-morbid historical assessment)ASPECT 3 6 confirmed by the pre-operation CT scandiagnosed with intracranial hemorrhagic diseases (including intracranial hemorrhage, subarachnoid hemorrhage, etc.)

- using any drugs related to NBP during onset between randomizationwith dysphagia at the onset of stroke
- history of coagulation dysfunction, systemic bleeding, neutropenia or thrombocytopenia
- history of chronic hepatopathy, liver or kidney dysfunction (3× upper limits of normal alanine transaminase or 2× upper limits of normal creatinine)
- history of severe cardio-pulmonary diseases judged by investigators
- history of bradycardia (heart rate < 60 beats/m) or sick sinus syndrome
- having severe non-cardiovascular comorbidity with life expectancy < 3 months or failed to follow the study for other reasonshistory of drug or food allergy, or were known to be allergic to the composition of drugs in this study
- contraindications for the digital subtraction angiography procedure, including severe allergy for contrast agent with or without iodine

- pregnancy or lactation, or childbearing women, with documented negative pregnancy test, but without reliable contraception
- incapable to follow this study for mental illness, cognitive or emotional disorders
- unsuitable for this study in the opinion of the investigators

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

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	Page 1, Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, Trial registration
	2b	All items from the World Health Organization Trial Registration Data Set	Refer to trial registration online
Protocol version	3	Date and version identifier	Page 13, Trial Status
Funding	4	Sources and types of financial, material, and other support	Page 14, Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15, Authors' contributions
	5b	Name and contact information for the trial sponsor	Page 1and 2, Corresponding Author
	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	Page 14,Funding

	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)	Page 15, “Authors’ contributions” and “Data and safety monitoring board”
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	Page 5, Background
	6b	Explanation for choice of comparators	Page 5, Background
Objectives	7	Specific objectives or hypotheses	Page 6, Background
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)	Page 6, Study Design
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	Page 6, Study Design
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)	Page 7, Participants and Page 21, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 7, Procedures
	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)	Page 8, Procedures

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 8, Procedures
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8, Procedures
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	Page 8, Outcomes
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)	Page 6, Study design and Page 1, Table 1
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	Page 10, Power and Sample Size Calculation
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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	Page 7, Randomization
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	Page 7, Randomization
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 7, Randomization

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 7, Randomization
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 7, Randomization
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	Page 8, Outcomes
	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	Page 8, Outcomes
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	Page 8, Outcomes
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	Page 10, Statistical Analyses
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	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)	Page 10, Statistical Analyses
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	Page 16, Data and safety monitoring board

	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	Page 10, Statistical Analyses
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11, Ethical considerations
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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7, Participants
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15, Competing interests
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	Page 15, Availability of data and material

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	N/A
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	Page 15, Availability of data and material
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	Page 19, Table 1

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

BMJ Open

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Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) Trial: Study Protocol for a Randomized Placebo-controlled Trial

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Abstract

Introduction: As a neuroprotective medication, butylphthalide (NBP) has been proven to may help protect against cerebral ischemic injury. However, evidence about whether NBP influences the outcomes of patients with acute ischemic stroke who are receiving revascularization treatment is limited. This study aims to evaluate whether additional NBP therapy can improve the functional outcome of patients who receive intravenous recombinant tissue plasminogen activator and/or endovascular treatment (EVT).

Methods and analysis: The study will be a randomized, double-blind, placebo-controlled, multiple-center, parallel group trial. The sample size is estimated at 1200 patients. Eligible patients will be randomized at a 1:1 ratio to receive either NBP or placebo daily for 90 d, which will include 14 d of injections and 76 d of capsules. The first use of NBP/placebo will be started within 6 h of the onset of ischemic stroke. The primary outcome is the functional outcome as assessed by the 90-d modified Rankin Scale, adjusted for the baseline of the National Institutes of Health Stroke Scale. The primary safety outcome is the percentage of serious adverse events during the 90 d of treatment. This trial will determine whether medication of NBP benefits patients with acute ischemic stroke who receive intravenous thrombolysis or EVT.

Ethics and dissemination: The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by several ethics committees including the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02. Results of the study will be published in peer-reviewed scientific journals and shared in scientific presentations.

Trial registration: NCT03539445; Registered May 29, 2018, https://www.clinicaltrials.gov/ct2/show/NCT03539445?term=NCT03539445&draw=2&rank=1

Keywords: Butylphthalide; Acute Ischemic Stroke; Intravenous Thrombolysis; Endovascular Treatment

Strengths and limitations of this study

- The BAST trial is a randomized, double-blind, placebo-controlled, multiple-center parallel group study aimed to assess the efficacy and safety of NBP in patients who received intravenous rt-PA, and/or EVT.

- This is the first study to determine whether the application of NBP could improve functional outcome of acute ischemic stroke patients receiving intravenous thrombolysis or EVT.

- Strict enrolling criteria including the first injection started within 6 hours from onset seem to be a challenge, which may result in a bias between primary stroke centers and comprehensive stroke centers.

- The BAST study is conducted in China only, and the results are limited to extrapolated to other ethic population.

Introduction

Ischemic stroke is the third leading cause of death globally because of its high prevalence, morbidity, and mortality[1 2]. Even received standard intravenous recombinant tissue plasminogen activator (rt-PA) or endovascular treatment (EVT), a large proportion of patients can't achieve functional independence[3-11]. The ESCAPE-NA1 (Efficacy and safety of nerinetide for the treatment of acute ischemic stroke) study showed that nerinetide had a therapeutic effect among patients who were not treated with intravenous thrombolysis[12]. Although this finding required confirmation, it suggests that neuroprotection in human stroke might be possible. Since then, neuroprotective medicine has attracted the attention of clinicians, with the aim of reducing neuronal damage and improving neurological deficits.

Butylphthalide (NBP), a well-known neuroprotective medication, is a family of compounds that has been isolated from the seeds of Apium graveolens Linn, of which the active ingredient is dl-3-N-NBP. NBP has been shown to reduce cerebral ischemic damage and improve clinical outcomes of patients. The underlying mechanisms have been confirmed in experimentation in animal and include promoting microcirculation[13]; protecting blood brain barrier[14]; releasing mitochondrial dysfunction[15], post stroke inflammation[16], and cerebral edema[17]. NBP has been approved for use in patients with ischemic stroke in China since 2002. Despite the recent development in reperfusion treatment for acute ischemic stroke, it remains uncertain whether combination therapy with NBP improves patient outcomes.

This protocol describes the rationale and design of the Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) trial, which aims to investigate whether NBP is an effective and safe medication for patients who receive intravenous rt-PA and EVT.

Methods/design

Study Design

The BAST trial will be a randomized, double-blind, placebo-controlled, multiple-center, parallel group study. It aims to assess the efficacy and safety of NBP in patients who receive intravenous rt-PA and/or EVT. Participants will be recruited from neurology or interventional neuroradiology departments from approximately 30 hospitals across China. Eligible patients will be randomized at a 1:1 ratio to receive either NBP or placebo daily for 90 d. They will be assessed at on the day of randomization, 2 d after the first injection, and on days 14, 30, 60 and 90 (Table 1). The BAST trial design is in compliance with the Declaration of Helsinki. All patients or his/ her legal representative will be asked to provide informed consent (see supplemental file). The BAST study has been registered at ClinicalTrials.gov (NCT03539445).

Objective

The primary objective of the trial is to determine whether administration of NBP

improves the functional outcome of acute ischemic stroke patients who receive intravenous thrombolysis or EVT.

Participants

All patients who arrive at the hospital presenting with sudden neurological function deficits will be recruited and screened for eligibility based on the inclusion and exclusion criteria (Table 2). The investigators fully inform the patient and/or legal representative of the equal opportunity to use the test medication or placebo, the prognosis of the disease, and the adverse reactions that can occur, which are ultimately weighed by the patient or relatives. Patients or their legal representative will provide informed consent prior to enrollment.

Randomization

The randomization procedure will be carried out using a computer-generated code and permuted blocks. This allows eligible patients to be assigned NBP or placebo at a 1:1 ratio. Patients will be assigned a random serial number based on their time of enrollment and provided with the corresponding medicine which are beforehand blind-covered. Both researchers and patients will be blind to the treatment.

Procedures

Eligible patients will receive adjunctive NBP/placebo treatment alongside standard intravenous rt-PA and/or EVT. Patients in the experimental group will receive NBP and a 100 ml sodium chloride injection twice/day during the initial 14 d and soft 0.2 g NBP capsules three times/day from day 15 to 90. The control group will receive a 100 ml

placebo injection twice/day during the initial 14 d and soft 0.2 g placebo capsules three times/day from day 15 to 90. The first NBP/placebo injection will be administered within 6 h of the onset of ischemic stroke. Patients will be recommended to continue the injections for 14 d and for a minimum of 10 d. The capsule administration will be started the day following the final injection, and patients will be recommended to continue taking the capsules until day 90. Each injection will last for at least 50 min and will be administered 6 h apart. Patients will be asked to take the capsules daily before meals and record medication administration, which will be checked by researchers. The steering committee will make recommendations for concomitant medications. All secondary preventive strategies, including antithrombosis and management of risk factors, will be followed according to guidelines. However, neuroprotective medications, such as uriklin, edaravone, and any ginkgo-containing injections will be prohibited.

Outcomes

Primary outcome

The primary efficacy outcome is the proportion of patients with a favorable outcome 90 d after randomization. A favorable outcome[18 19] will be defined as a score of 0 on the modified Rankin Scale (mRS) in patients with a baseline score of 3–7 on the National Institutes of Health Stroke Scale (NIHSS); an mRS score of 0–1 in patients with a baseline NIHSS score of 8–14; and an mRS score of 0–2 in patients with a baseline NIHSS score of 15–22.

We will perform a prespecified subgroup analysis to estimate the effects of sex, age, baseline NIHSS, history of hypertension, diabetes, etiological subgroups, and the use of

EVT, to determine the homogeneity of treatment effects in these subgroups.

Secondary outcomes

The secondary efficacy outcomes will include: the difference value of the NIHSS scores between baseline and days 14 and 90; the cerebral infarction volume at day 14; the recanalization rate within the first 24 h of treatment; the percentage of symptomatic intracranial hemorrhage within the first 24 hours; recurrent symptomatic ischemic stroke and vascular events during the 90 d of treatment; any vascular complications due to vascular events (recurrent symptomatic ischemic stroke, myocardiac infarction, or vascular death) at day 90; the life quality score estimated by EuroQol 5D at day 90; cognitive function estimated by Mini-mental State Examination and Montreal Cognitive Assessment Scales at day 90; rate of favorable outcome at day 14.

Safety outcomes

The primary safety outcome is the percentage of serious adverse events during the 90 d of treatment, which includes any events resulting in prolonging-hospital time, permanent damage to the body system/organ, a life-threatening condition, or death. The secondary outcomes will include symptomatic intracranial hemorrhage during 90 d of treatment; total mortality between day 14 and 90, adverse events between day 14 and 90, and serious adverse events within the first 14 d of treatment.

Power and Sample Size Calculation

According to previous study[20], we predict that the rate of the 90-day favorable outcome (based on adjusted mRS scores) will be 60% in the experimental group and 50% in the

control group. The test level will be set at 0.05. To achieve 90% power and a significance level of 0.05 (two-tailed), each group will require 550 patients. Assuming a dropout rate of 10%, 600 patients will be required for each group, for a total of 1200 patients in the trial.

Statistical Analyses

The primary analysis will be based on the intention to treat principle. Primary efficacy in the two groups will be compared using Chi-square test, and logistic regression will be used to calculate the odds ratio and 95% confidence interval. Missing outcome data will be imputed using the last observation carried forward method. Significance will be set at 0.05 and all statistical tests will be two-tailed. Furthermore, when 50% and 75% of participants have completed follow-up, formal interim analyses of the primary outcome will be conducted to determine overwhelming efficacy or futility; in this cases, we will consider stopping the trial. Overwhelming efficacy will be estimated using the O'Brien-Fleming boundaries on the binary outcome of the 90-day favorable outcome, with corresponding significance levels of 0.003, 0.018, and 0.044.

Patient and Public Involvement

Patients will not be involved in the development of the research question, selection of outcome measures, design of the trial, recruitment of participants, or conduct of the trial. Results of the trial will be disseminated to study participants through direct consultation with a trial clinician at completion of the trial as well as through the publication of the results.

Ethical dissemination

The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02.

Discussion

The BAST trial will be a phase III randomized controlled study. It will be carried out in a Chinese population. This trial will explore the efficacy and safety of NBP, a typical neuroprotective medication, for patients with acute ischemic stroke who receive intravenous rt-PA and endovascular treatment.

Several reports[20-24] indicated that NBP may have a beneficial effect on patients with ischemic stroke. A multi-center, randomized, double-blind and placebo-control study showed that the NBP treatment significantly improved the neurofunctional deficits, and the two groups did not significantly differ in the rate of adverse events [25]. A systematic review that included 21 randomized controlled trials reported that NBP improves neurological function after acute ischemic stroke and appears to be a safe treatment[26]. Another systematic review that included 12 randomized controlled trials reported that the combined use of NBP and standard anti-ischemic stroke drugs was more effective than the use of standard drugs alone[27]. In this study, we will further explore the efficacy and safety of BNP in patients who receive intravenous rt-PA and/or EVT.

An vitro experiment has demonstrated that NBP can protect endothelial cells against xidative/nitrosative stress and subsequent cell death by enhancing hypoxia inducible factor-1 alpha expression[28]. The protective effect of NBP on mitochondrial function has been demonstrated in early animal studies, which showed that NBP improves the activity of Na^+/K^+-ATPase and Ca_2^+-ATPase in mitochondria[29]. NBP has also been found to prevent the occurrence of ischemic stroke via the improvement of cerebral microcirculaition in stroke-prone renovascular hypertensive rats[30]. NBP administration ameliorated the reperfusion-induced brain damage via the enhancement of hepatocyte growth factor and the inhibition of TLR4/NF-kB and pro-inflammatory cytokines in vivo and in vitro[31]. Additionally, many recent studies have shown that treatment with NBP influences the level of proteins, such as caspase-3 and caspase-9, in the execution phase of cell apoptosis[29]. This finding offers a potential approach toward the prevention of further cellular death in the ischemic penumbra. Above all, NBP protects against ischemic cerebral injury through several mechanisms, which include alleviating oxidative damage, regulating mitochondrial dysfunction, improving microcirculation, and inhibiting apoptosis and the inflammatory response. These NBP effects provide the theoretical basis of this study. We speculate that NBP will play a role in preventing ischemia reperfusion injury after intravenous rt-PA and endovascular treatment, and that combination therapy will improve patients' functional outcomes.

One strength of this study is the requirement of NBP/placebo to be administrated within 6h from onset of the ischemic stroke. Treatment with intravenous rt-PA is administered within 4.5 h, and endovascular treatment is administered within 6 h. Therefore, in our trial, neuroprotective treatment will be synchronized with the recanalization treatment. It is well-documented that almost immediately after vascular occlusion occurs, ischemic cerebral injury begins. Moreover, reperfusion injury after recanalization may sometimes aggravate tissue damage. In most previous studies[21], neuroprotective medicine is administered within 48 h of stroke onset. However, we will administer the neuroprotective treatment in the superacute ischemic injury phase, which will enable us to demonstrate whether patients who receive combination therapy during this phase achieve a better functional outcome..

This study has some limitations. The sample size is estimated at 1200 patients, which is considered relatively small for a phase III intervention trial. Nevertheless, this conservative estimate will allow us to estimate the primary outcome parameter with sufficient precision. Strict procedures, such as first injection within 6 h from onset, will be a challenge for patient selection and may result in a bias between primary stroke centers and comprehensive stroke centers. Finally, the BAST study will be conducted in China only, and the results may not limited to generalize to other populations.

List of abbreviations

BAST, Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment; LOCF, last observation carried forward; mRS,

modified Rankin Scale score; NBP, butylphthalide; NIHSS, the National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.

Authors' contributions

All authors participated in the conception and design of the study. All authors are responsible for the patients' enrolment and data acquisition in their institution. All authors approved the final manuscript version, and accounted for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work were appropriately investigated and resolved. All authors have read and approved the manuscript.

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Competing interests statement

The authors declare that they have no competing interests.

Trial Status

The current protocol version 21.0, 12 December 2019. This trial is in the process of recruiting participants. The actual trial enrolment started on **1** July 2018. We expect to enroll the target sample size by September 2022 and plan to continue with follow-up until December 2022.

Consent for publication

Not applicable.

Availability of data and material

The data generated from this study will be made available on reasonable request and approval by the corresponding author.

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None.

Data and safety monitoring board

The data safety and monitoring board will monitor the progress of the study to ensure the patient safety and the highest standards of ethics. Annual monitoring will be performed by an independent clinical monitor. Interim progress reports will be sent to the academic committee.

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Table 1. The visit plan.

Measures	**Baseline**	**Day 2**	**Day 14**	**Day 30**	**Day 60**	**Day 90**
Demographics	×					
History of present illness	×					
mRS	×	×	×	×	×	×
Previous history	×					
Medication	×		×	×	×	×
NIHSS	×	×	×			×
Head CT	×					
Head MRI			×			
ASPECT	×					
Lab examination	×		×			
Electrocardiograph	×					
Inclusion & exclusion criteria	×					
Informed consent	×					
randomization	×					
Injection	×					
Compliance			×	×	×	×
Special lab test		×	×			×
TOAST classification			×			
OCSP classification	×					
EQ-5D				×	×	×
MMSE			×			×

MoCA			×			×
Soft capsules			×			
AE/SAE		×	×	×	×	×
*including at least test of blood glucose, blood routine examination (count of platelet), renal and liver function (alanine transaminase, aspartate aminotransferase and creatinine)						

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECT: Alberta Stroke Program Early CT Score; TOAST: Trial of Org 10 172 in acute Stroke Treatment; OCSP: Oxfordshire Community Stroke Programme; EQ-5D: EuroQol 5D; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; AE/SAE: Adverse Event /Serious Adverse Event .

Table 2. Inclusion and exclusion criteria for the BAST study

Inclusion Criteria
● age ≥18 years
● diagnosed with acute ischemic stroke
● within 6 hours from symptom onset
● baseline NIHSS score ranging 4 from 25
● receiving intravenous rt-PA, or endovascular treatment (including intraarterial thrombolysis and mechanical thrombectomy), or intravenous rt-PA bridging endovascular treatment
● signing informed consent
Exclusion Criteria
● Modified Rankin Scale (mRS) >1 at randomization (pre-morbid historical assessment)ASPECT ≤ 6 confirmed by the pre-operation CT scandiagnosed with intracranial hemorrhagic diseases (including intracranial hemorrhage, subarachnoid hemorrhage, etc.)

- Already use NBP or any drugs containing NBP between onset and randomization
- Appeared with dysphagia before randomization
- With a history of coagulation disorders, hemorrhagic diathesis, neutropenia or thrombocytopenia
- With a history of chronic hepatopathy, liver or kidney dysfunction (≥ 3× upper limits of normal alanine transaminase or ≥ 2× upper limits of normal creatinine)
- With a history of severe cardio-pulmonary diseases judged by investigators
- With a history of bradycardia (heart rate < 60 beats/m) or sick sinus syndrome
- Having severe non-cardiovascular comorbidity with life expectancy < 3 months or failed to follow the study for other reasonshistory of drug or food allergy, or were known to be allergic to the composition of drugs in this study

- Contraindications for the digital subtraction angiography procedure, including severe allergy for contrast agent with or without iodine
- Pregnancy or lactation, or childbearing women, with documented negative pregnancy test, but without reliable contraception
- Incapable to follow this study for mental illness, cognitive or emotional disorders
- Unsuitable for this study in the opinion of the investigators

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

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	Page 1, Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, Trial registration
	2b	All items from the World Health Organization Trial Registration Data Set	Refer to trial registration online
Protocol version	3	Date and version identifier	Page 13, Trial Status
Funding	4	Sources and types of financial, material, and other support	Page 14, Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15, Authors' contributions
	5b	Name and contact information for the trial sponsor	Page 1and 2, Corresponding Author
	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	Page 14,Funding

	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)	Page 15, “Authors’ contributions” and “Data and safety monitoring board”
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	Page 5, Background
	6b	Explanation for choice of comparators	Page 5, Background
Objectives	7	Specific objectives or hypotheses	Page 6, Background
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)	Page 6, Study Design
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	Page 6, Study Design
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)	Page 7, Participants and Page 21, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 7, Procedures
	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)	Page 8, Procedures

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 8, Procedures
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8, Procedures
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	Page 8, Outcomes
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)	Page 6, Study design and Page 1, Table 1
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	Page 10, Power and Sample Size Calculation
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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	Page 7, Randomization
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	Page 7, Randomization
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 7, Randomization

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 7, Randomization
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 7, Randomization
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	Page 8, Outcomes
	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	Page 8, Outcomes
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	Page 8, Outcomes
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	Page 10, Statistical Analyses
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	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)	Page 10, Statistical Analyses
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	Page 16, Data and safety monitoring board

	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	Page 10, Statistical Analyses
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11, Ethical considerations
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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 7, Participants
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15, Competing interests
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	Page 15, Availability of data and material

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	N/A
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	Page 15, Availability of data and material
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	Page 19, Table 1

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

BMJ Open

Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) Trial: Study Protocol for a Randomized Placebo-controlled Trial

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Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) Trial: Study Protocol for a Randomized Placebo-controlled Trial

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Abstract

Introduction: As a neuroprotective medication, butylphthalide (NBP) may help protect against cerebral ischemic injury. However, evidence about whether NBP influences the outcomes of patients with acute ischemic stroke who are receiving revascularization treatment is limited. This study aims to evaluate whether additional NBP therapy can improve the functional outcome of patients who receive intravenous recombinant tissue plasminogen activator and/or endovascular treatment (EVT).

Methods and analysis: The study will be a randomized, double-blind, placebo-controlled, multiple-center, parallel group trial. The sample size is estimated at 1200 patients. Eligible patients will be randomized at a 1:1 ratio to receive either NBP or placebo daily for 90 d, which will include 14 d of injections and 76 d of capsules. The first use of NBP/placebo will be started within 6 h of the onset of ischemic stroke. The primary outcome is the functional outcome as assessed by the 90-d modified Rankin Scale, adjusted for the baseline of the National Institutes of Health Stroke Scale. The primary safety outcome is the percentage of serious adverse events during the 90 d of treatment. This trial will determine whether medication of NBP benefits patients with acute ischemic stroke who receive intravenous thrombolysis or EVT.

Ethics and dissemination: The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02. Ethics committees of all the participating sites have approved the study and that the names of all the ethics committees can be found in

the supplementary information (see supplementary file 1). Results of the study will be published in peer-reviewed scientific journals and shared in scientific presentations.

Trial registration: NCT03539445; Registered May 29, 2018, https://www.clinicaltrials.gov/ct2/show/NCT03539445?term=NCT03539445&draw=2&rank=1

Keywords: Butylphthalide; Acute Ischemic Stroke; Intravenous Thrombolysis; Endovascular Treatment

Strengths and limitations of this study

- The BAST trial is a randomized, double-blind, placebo-controlled, multiple-center parallel group study aimed to assess the efficacy and safety of NBP in patients who received intravenous rt-PA, and/or EVT.

- This is the first study to determine whether the application of NBP could improve functional outcome of acute ischemic stroke patients receiving intravenous thrombolysis or EVT.

- Strict enrolling criteria including the first injection started within 6 hours from onset seem to be a challenge, which may result in a bias between primary stroke centers and comprehensive stroke centers.

- The BAST study is conducted in China only, and the results are limited to extrapolated to other ethic population.

Introduction

Ischemic stroke is the third leading cause of death globally because of its high prevalence, morbidity, and mortality[1 2]. Even received standard intravenous recombinant tissue plasminogen activator (rt-PA) or endovascular treatment (EVT), a large proportion of patients can't achieve functional independence[3-11]. The ESCAPE-NA1 (Efficacy and safety of nerinetide for the treatment of acute ischemic stroke) study showed that nerinetide had a therapeutic effect among patients who were not treated with intravenous thrombolysis[12]. Although this finding required confirmation, it suggests that neuroprotection in human stroke might be possible. Since then, neuroprotective medicine has attracted the attention of clinicians, with the aim of reducing neuronal damage and improving neurological deficits.

Butylphthalide (NBP), which may have potential as a neuroprotective medication, is a family of compounds that has been isolated from the seeds of Apium graveolens Linn, of which the active ingredient is dl-3-N-NBP. NBP has been shown to reduce cerebral ischemic damage and improve clinical outcomes of patients. The underlying mechanisms have been confirmed in experimentation in animal and include promoting microcirculation[13]; protecting blood brain barrier[14]; releasing mitochondrial dysfunction[15], post stroke inflammation[16], and cerebral edema[17]. NBP has been approved for use in patients with ischemic stroke in China since 2002. Despite the recent development in reperfusion treatment for acute ischemic stroke, it remains uncertain whether combination therapy with NBP improves patient outcomes.

This protocol describes the rationale and design of the Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) trial, which aims to investigate whether NBP is an effective and safe medication for patients who receive intravenous rt-PA and EVT.

Methods/design

Study Design

The BAST trial will be a randomized, double-blind, placebo-controlled, multiple-center, parallel group study. It aims to assess the efficacy and safety of NBP in patients who receive intravenous rt-PA and/or EVT. Participants will be recruited from neurology or interventional neuroradiology departments from approximately 30 hospitals across China. Eligible patients will be randomized at a 1:1 ratio to receive either NBP or placebo daily for 90 d. They will be assessed at on the day of randomization, 2 d after the first injection, and on days 14, 30, 60 and 90 (Table 1). The BAST trial design is in compliance with the Declaration of Helsinki. All patients or his/ her legal representative will be asked to provide informed consent (see supplementary file 2). The BAST study has been registered at ClinicalTrials.gov (NCT03539445).

Objective

The primary objective of the trial is to determine whether administration of NBP

improves the functional outcome of acute ischemic stroke patients who receive intravenous thrombolysis or EVT.

Participants

All patients who arrive at the hospital presenting with sudden neurological function deficits will be recruited and screened for eligibility based on the inclusion and exclusion criteria (Table 2). The investigators fully inform the patient and/or legal representative of the equal opportunity to use the test medication or placebo, the prognosis of the disease, and the adverse reactions that can occur, which are ultimately weighed by the patient or relatives. Patients or their legal representative will provide informed consent prior to enrollment.

Randomization

The randomization procedure will be carried out using a computer-generated code and permuted blocks. This allows eligible patients to be assigned NBP or placebo at a 1:1 ratio. Patients will be assigned a random serial number based on their time of enrollment and provided with the corresponding medicine which are beforehand blind-covered. Both researchers and patients will be blind to the treatment.

Procedures

Eligible patients will receive adjunctive NBP/placebo treatment alongside standard intravenous rt-PA and/or EVT. Patients in the experimental group will receive NBP and a 100 ml sodium chloride injection twice/day during the initial 14 d and soft 0.2 g NBP capsules three times/day from day 15 to 90. The control group will receive a 100 ml

placebo injection twice/day during the initial 14 d and soft 0.2 g placebo capsules three times/day from day 15 to 90. The first NBP/placebo injection will be administered within 6 h of the onset of ischemic stroke. Patients will be recommended to continue the injections for 14 d and for a minimum of 10 d. The capsule administration will be started the day following the final injection, and patients will be recommended to continue taking the capsules until day 90. Each injection will last for at least 50 min and will be administered 6 h apart. Patients will be asked to take the capsules daily before meals and record medication administration, which will be checked by researchers. The steering committee will make recommendations for concomitant medications. All secondary preventive strategies, including antithrombosis and management of risk factors, will be followed according to guidelines. However, neuroprotective medications, such as uriklin, edaravone, and any ginkgo-containing injections will be prohibited.

Outcomes

Primary outcome

The primary efficacy outcome is the proportion of patients with a favorable outcome 90 d after randomization. A favorable outcome[18 19] will be defined as a score of 0 on the modified Rankin Scale (mRS) in patients with a baseline score of 3–7 on the National Institutes of Health Stroke Scale (NIHSS); an mRS score of 0–1 in patients with a baseline NIHSS score of 8–14; and an mRS score of 0–2 in patients with a baseline NIHSS score of 15–22.

We will perform a prespecified subgroup analysis to estimate the effects of sex, age, baseline NIHSS, history of hypertension, diabetes, etiological subgroups, and the use of

EVT, to determine the homogeneity of treatment effects in these subgroups.

Secondary outcomes

The secondary efficacy outcomes will include: the difference value of the NIHSS scores between baseline and days 14 and 90; the cerebral infarction volume at day 14; the recanalization rate within the first 24 h of treatment; the percentage of symptomatic intracranial hemorrhage within the first 24 hours; recurrent symptomatic ischemic stroke and vascular events during the 90 d of treatment; any vascular complications due to vascular events (recurrent symptomatic ischemic stroke, myocardiac infarction, or vascular death) at day 90; the life quality score estimated by EuroQol 5D at day 90; cognitive function estimated by Mini-mental State Examination and Montreal Cognitive Assessment Scales at day 90; rate of favorable outcome at day 14.

Safety outcomes

The primary safety outcome is the percentage of serious adverse events during the 90 d of treatment, which includes any events resulting in prolonging-hospital time, permanent damage to the body system/organ, a life-threatening condition, or death. The secondary outcomes will include symptomatic intracranial hemorrhage during 90 d of treatment; total mortality between day 14 and 90, adverse events between day 14 and 90, and serious adverse events within the first 14 d of treatment.

Power and Sample Size Calculation

According to previous study[20], we predict that the rate of the 90-day favorable outcome (based on adjusted mRS scores) will be 60% in the experimental group and 50% in the

control group. The test level will be set at 0.05. To achieve 90% power and a significance level of 0.05 (two-tailed), each group will require 550 patients. Assuming a dropout rate of 10%, 600 patients will be required for each group, for a total of 1200 patients in the trial.

Statistical Analyses

The primary analysis will be based on the intention to treat principle. Primary efficacy in the two groups will be compared using Chi-square test, and logistic regression will be used to calculate the odds ratio and 95% confidence interval. Missing outcome data will be imputed using the last observation carried forward method. Significance will be set at 0.05 and all statistical tests will be two-tailed. Furthermore, when 50% and 75% of participants have completed follow-up, formal interim analyses of the primary outcome will be conducted to determine overwhelming efficacy or futility; in this cases, we will consider stopping the trial. Overwhelming efficacy will be estimated using the O'Brien-Fleming boundaries on the binary outcome of the 90-day favorable outcome, with corresponding significance levels of 0.003, 0.018, and 0.044.

Patient and Public Involvement

Patients will not be involved in the development of the research question, selection of outcome measures, design of the trial, recruitment of participants, or conduct of the trial. Results of the trial will be disseminated to study participants through direct consultation with a trial clinician at completion of the trial as well as through the publication of the results.

Ethics and Dissemination

The protocol was written according to the general ethical guidelines of the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of Beijing Tiantan Hospital, Capital Medical University with the approval number KY 2018-003-02. Ethics committees of all the participating sites have approved the study and that the names of all the ethics committees can be found in the supplementary information (see supplementary file 1). Results of the study will be published in peer-reviewed scientific journals and shared in scientific presentations.

Discussion

The BAST trial will be a phase III randomized controlled study. It will be carried out in a Chinese population. This trial will explore the efficacy and safety of NBP, a potential neuroprotective medication, for patients with acute ischemic stroke who receive intravenous rt-PA and endovascular treatment.

Several reports[20-24] indicated that NBP may have a beneficial effect on patients with ischemic stroke. A multi-center, randomized, double-blind and placebo-control study showed that the NBP treatment significantly improved the neurofunctional deficits, and the two groups did not significantly differ in the rate of adverse events [25]. A systematic review that included 21 randomized controlled trials reported that NBP improves neurological function after acute ischemic stroke and appears to be a safe treatment[26].

Another systematic review that included 12 randomized controlled trials reported that the combined use of NBP and standard anti-ischemic stroke drugs was more effective than the use of standard drugs alone[27]. In this study, we will further explore the efficacy and safety of BNP in patients who receive intravenous rt-PA and/or EVT.

An vitro experiment has demonstrated that NBP can protect endothelial cells against xidative/nitrosative stress and subsequent cell death by enhancing hypoxia inducible factor-1 alpha expression[28]. The protective effect of NBP on mitochondrial function has been demonstrated in early animal studies, which showed that NBP improves the activity of Na^+/K^+-ATPase and Ca_2^+-ATPase in mitochondria[29]. NBP has also been found to prevent the occurrence of ischemic stroke via the improvement of cerebral microcirculaition in stroke-prone renovascular hypertensive rats[30]. NBP administration ameliorated the reperfusion-induced brain damage via the enhancement of hepatocyte growth factor and the inhibition of TLR4/NF-kB and pro-inflammatory cytokines in vivo and in vitro[31]. Additionally, many recent studies have shown that treatment with NBP influences the level of proteins, such as caspase-3 and caspase-9, in the execution phase of cell apoptosis[29]. This finding offers a potential approach toward the prevention of further cellular death in the ischemic penumbra. Above all, NBP protects against ischemic cerebral injury through several mechanisms, which include alleviating oxidative damage, regulating mitochondrial dysfunction, improving microcirculation, and inhibiting apoptosis and the inflammatory response. These NBP effects provide the theoretical basis of this study. We speculate that NBP will play a role in preventing ischemia reperfusion injury after intravenous rt-PA and endovascular treatment, and that

combination therapy will improve patients' functional outcomes.

One strength of this study is the requirement of NBP/placebo to be administrated within 6h from onset of the ischemic stroke. Treatment with intravenous rt-PA is administered within 4.5 h, and endovascular treatment is administered within 6 h. Therefore, in our trial, neuroprotective treatment will be synchronized with the recanalization treatment. It is well-documented that almost immediately after vascular occlusion occurs, ischemic cerebral injury begins. Moreover, reperfusion injury after recanalization may sometimes aggravate tissue damage. In most previous studies[21], neuroprotective medicine is administered within 48 h of stroke onset. However, we will administer the neuroprotective treatment in the superacute ischemic injury phase, which will enable us to demonstrate whether patients who receive combination therapy during this phase achieve a better functional outcome..

This study has some limitations. The sample size is estimated at 1200 patients, which is considered relatively small for a phase III intervention trial. Nevertheless, this conservative estimate will allow us to estimate the primary outcome parameter with sufficient precision. Strict procedures, such as first injection within 6 h from onset, will be a challenge for patient selection and may result in a bias between primary stroke centers and comprehensive stroke centers. Finally, the BAST study will be conducted in China only, and the results may not limited to generalize to other populations.

List of abbreviations

BAST, Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment; LOCF, last observation carried forward; mRS, modified Rankin Scale score; NBP, butylphthalide; NIHSS, the National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.

Authors' contributions

All authors participated in the conception and design of the study. XZ, AW, JZ, YZ are responsible for the patients' enrolment and data acquisition. AW, YZ, XT contributed to the data analysis plan. BJ, XH, YW and ZM accounted for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work were appropriately investigated and resolved. XZ and AW prepared the first draft of the manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests statement

The authors declare that they have no competing interests.

Trial Status

The current protocol version 21.0, 12 December 2019. This trial is in the process of recruiting participants. The actual trial enrolment started on **1** July 2018. We expect to enroll the target sample size by September 2022 and plan to continue with follow-up until December 2022.

Consent for publication

Not applicable.

Availability of data and material

The data generated from this study will be made available on reasonable request and approval by the corresponding author.

Acknowledgements

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Data and safety monitoring board

The data safety and monitoring board will monitor the progress of the study to ensure the patient safety and the highest standards of ethics. Annual monitoring will be performed by an independent clinical monitor. Interim progress reports will be sent to the academic committee.

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Table 1. The visit plan.

Measures	**Baseline**	**Day 2**	**Day 14**	**Day 30**	**Day 60**	**Day 90**
Demographics	×					
History of present illness	×					
mRS	×	×	×	×	×	×
Previous history	×					
Medication	×		×	×	×	×
NIHSS	×	×	×			×
Head CT	×					
Head MRI			×			
ASPECT	×					
Lab examination	×		×			
Electrocardiograph	×					
Inclusion & exclusion criteria	×					
Informed consent	×					
randomization	×					
Injection	×					
Compliance			×	×	×	×
Special lab test		×	×			×
TOAST classification			×			
OCSP classification	×					
EQ-5D				×	×	×
MMSE			×			×

MoCA			×			×
Soft capsules			×			
AE/SAE		×	×	×	×	×
*including at least test of blood glucose, blood routine examination (count of platelet), renal and liver function (alanine transaminase, aspartate aminotransferase and creatinine)						

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECT: Alberta Stroke Program Early CT Score; TOAST: Trial of Org 10 172 in acute Stroke Treatment; OCSP: Oxfordshire Community Stroke Programme; EQ-5D: EuroQol 5D; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; AE/SAE: Adverse Event /Serious Adverse Event .

Table 2. Inclusion and exclusion criteria for the BAST study

Inclusion Criteria
● age ≥18 years
● diagnosed with acute ischemic stroke
● within 6 hours from symptom onset
● baseline NIHSS score ranging 4 from 25
● receiving intravenous rt-PA, or endovascular treatment (including intraarterial thrombolysis and mechanical thrombectomy), or intravenous rt-PA bridging endovascular treatment
● signing informed consent
Exclusion Criteria
● Modified Rankin Scale (mRS) >1 at randomization (pre-morbid historical assessment)ASPECT ≤ 6 confirmed by the pre-operation CT scandiagnosed with intracranial hemorrhagic diseases (including intracranial hemorrhage, subarachnoid hemorrhage, etc.)

- Already use NBP or any drugs containing NBP between onset and randomization
- Appeared with dysphagia before randomization
- With a history of coagulation disorders, hemorrhagic diathesis, neutropenia or thrombocytopenia
- With a history of chronic hepatopathy, liver or kidney dysfunction (≥ 3× upper limits of normal alanine transaminase or ≥ 2× upper limits of normal creatinine)
- With a history of severe cardio-pulmonary diseases judged by investigators
- With a history of bradycardia (heart rate < 60 beats/m) or sick sinus syndrome
- Having severe non-cardiovascular comorbidity with life expectancy < 3 months or failed to follow the study for other reasonshistory of drug or food allergy, or were known to be allergic to the composition of drugs in this study

- Contraindications for the digital subtraction angiography procedure, including severe allergy for contrast agent with or without iodine
- Pregnancy or lactation, or childbearing women, with documented negative pregnancy test, but without reliable contraception
- Incapable to follow this study for mental illness, cognitive or emotional disorders
- Unsuitable for this study in the opinion of the investigators

mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.

	Names of Ethics Committee
1	Ethics Committee of Traditional Chinese Medicine Hospital of Guangdong Province
2	Ethics Committee of Tianjin TEDA Hospital
3	Ethics Committee of Beijing Tiantan Hospital
4	Ethics Committee of Langfang Changzheng Hospital
5	Ethics Committee of Nanning Second People's Hospital
6	Ethics Committee of Wuhan Central Hospital
7	Ethics Committee of Qian Wei Hospital of Jilin Province
8	Ethics Committee of Nanshi Hospital of Nanyang
9	Ethics Committee of Liaocheng Brain Hospital
10	Ethics Committee of Qingdao Central Hospital
11	Ethics Committee of Tianjin Xiqing Hospital
12	Ethics Committee of Jilin Province People’s Hospital
13	Ethics Committee of The Fourth Affiliated Hospital of China Medical University
14	Ethics Committee of Nanhua Hospital Affiliated to Nanhua University
15	Ethics Committee of Tianjin Binhai Hospital
16	Ethics Committee of Loudi Central Hospital
17	Ethics Committee of Liuzhou Workers' Hospital
18	Ethics Committee of Shenzhen Hospital South Medical University
19	Ethics Committee of Liaocheng No. 3 People's Hospital
20	Ethics Committee of Northern Theater Command General Hospital
21	Ethics Committee of West China Hospital，Sichuan University
22	Ethics Committee of Hunan Province People’s Hospital
23	Ethics Committee of Nanning First People's Hospital
24	Ethics Committee of Meizhou People’s Hospital
25	Ethics Committee of The First Affiliated Hospital of Wannan Medical Hospital
26	Ethics Committee of Nanjing First Hospital
27	Ethics Committee of Anyang District Hospital
28	Ethics Committee of Huaian Second People’s Hospital
29	Ethics Committee of Traditional Chinese Medicine Hospital of Hunan Province
30	Ethics Committee of Wuxi People’s Hospital
31	Ethics Committee of Yunnan Kungang Hospital

32	Ethics Committee o Huizhou Central Hospital
33	Ethics Committee of Brain Hospital of Hunan Province
34	Ethics Committee of Cangzhou People's Hospital
35	Ethics Committee of Jiaozuo People's Hospital
36	Ethics Committee of Jingjiang People's Hospital
37	Ethics Committee of the People's Hospital of Jizhou District, Tianjin
38	Ethics Committee of Mianyang Central Hospital
39	Ethics Committee of The First Hospital of Kunming
40	Ethics Committee of Tianjin Forth Central Hospital
41	Ethics Committee of The Second People's Hospital of Jiaozuo
42	Ethics Committee of Guangzhou Panyu Central Hospital
43	Ethics Committee of the People's Hospital of Anning Yunnan

Informed consent form

Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment (BAST) Trial

You will be invited to participate in a clinical study, which is sponsored by Beijing Tiantan Hospital, Capital Medical University, and conducted in about 30 hospitals of China. This informed consent gives you some information to help you decide whether to participate in this clinical study or not. Please read it carefully. If you have any questions, please ask the researchers responsible for the study.

Your participation in this study is voluntary. This study has been reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital and all the participating sites. If you have questions related to the subjects' rights and interests, please contact the Ethics Committee of Beijing Tiantan Hospital at 010-67098551.

1. Purpose of the study: As a neuroprotective medication, butylphthalide (NBP) may help to protect against cerebral ischemic injury. However, evidence about whether NBP influences the outcomes of patients with acute ischemic stroke who are receiving revascularization treatment is limited. This study aims to evaluate whether additional NBP therapy can improve the functional outcome of patients who receive intravenous recombinant tissue plasminogen activator and/or endovascular treatment (EVT).
2. Process of the study: If you agree to participate in this study and sign the consent, we will number each participant and create a medical record file. You will be randomized at a 1:1 ratio to receive either NBP or placebo daily for 90 d alongside standard intravenous rt-PA and/or EVT, which will include 14 d of injections and 76 d of capsules. You will be visited on phone at 30 d and 60 d, and face-to-face at 90 d to collect your health condition according to medical scales.
3. Risk and discomfort: Possible risks of the study might be allergy to NBP or placebo and other adverse reactions including hepatic injury, nausea and psychiatric symptoms. In case of complications, we will take appropriate measures for

treatment in a timely manner. You can receive free treatment and/or compensation if there is any harm associated with the clinical study, and you also have the right to suspend treatment at any time.

4. Benefits received as a participant: The result of the study will give an answer to the question that weather NBP will improve the functional outcome of patients who receive intravenous recombinant tissue plasminogen activator and/or EVT. Besides, your health condition will be closely monitored by the doctor and all the NBP or placebo used during the study will be free of charge.
5. Responsibilities should be followed as a participant: Once participate in this research, you have the responsibility to provide true information about your medical history and current physical condition. Take the study drugs as instructions, and not to take restricted drugs. Inform your study doctor timely of any discomfort during the study period.
6. Privacy issue: If you decide to participate in this study, your personal data and during the study are confidential. All your information will be identified by a study number rather than your name, and will not be disclosed to anyone other than the members of research group. To ensure that the study is conducted in accordance with the regulations, if necessary, members of the government management department or the ethics review committee may refer to your personal data in the research as required. When the results of this study are published, no information about you will be disclosed.

You may choose not to participate in this study, or at any time inform the researcher to request withdrawal from the study. Your data will not be included in the study results, and any medical treatment and benefits will not be affected.

If you need additional treatment, or if you don't follow the study plan, or if you have any injuries related to the study or for any other reason, the investigator may terminate your continued participation in the study.

Signature for Consent

I have read an informed consent form.

I have the opportunity to ask questions and all questions have been answered.

I understand that participation in this study is voluntary.

I can choose not to participate in this study, or quit at any time after informing the researcher without any discrimination or reprisals, and my medical treatment and rights will not be affected.

If I need other treatment, or if I don't follow the study plan, or if there is any injury related to the study or if there is any other reason, the research physician may terminate my involvement in this study.

I will receive a signed copy of the informed consent.

Patient's name: _____

Signature of patient: _____

Signature of the agent of patient: _____

Date: _____

I have accurately informed the subject of this document that he/she has read this informed consent and has demonstrated that the subject has the opportunity to ask questions. I certify that he/she consented voluntarily.

Researcher's name: _____

Signature of researcher: _____

Date: _____

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	Page 1, Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, Trial registration
	2b	All items from the World Health Organization Trial Registration Data Set	Refer to trial registration online
Protocol version	3	Date and version identifier	Page 16, Trial Status
Funding	4	Sources and types of financial, material, and other support	Page 15, Funding statement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 15, Authors' contributions
	5b	Name and contact information for the trial sponsor	Page 1, Corresponding Author

	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	Page 15, Funding statement; Page 15, Authors' contributions
	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)	Page 15, Authors' contributions Page 16, Data and safety monitoring board
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	Page 6, Introduction
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	Page 7, Objective
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)	Page 7, Study Design
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	Page 7, Study Design
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)	Page 8, Participants and Page 24, Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8, Procedures

	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)	Page 8, Procedures
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9, Procedures
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9, Procedures
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	Page 9, Outcomes
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)	Page 7, Study design and Page 22, Table 1
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	Page 10, Power and Sample Size Calculation
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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	Page 8, Randomization
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	Page 8, Randomization

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 8, Randomization
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 8, Randomization
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 8, Randomization
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	Page 9, Outcomes
	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	Page 9, Outcomes
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	Page 9, Outcomes
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	Page 11, Statistical Analyses
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 9, Primary outcome
	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)	Page 11, Statistical Analyses
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	Page 16, Data and safety monitoring board
	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	Page 11, Statistical Analyses
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	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 12, Ethics and dissemination
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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8, Participants
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15, Competing interests statement

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	Page 16, Availability of data and material
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	N/A
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	Page 16, Availability of data and material
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	supplemental file 2
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	N/A

*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.