A Clinical Study on Tanhuo Decoction in the Treatment of Acute Coronary Syndrome Combined With Cerebral Atherosclerosis in the Elderly

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Research Summary

This project aims to evaluate the efficacy of Tanhuo Decoction in treating comorbid inflammation in elderly patients with Acute Coronary Syndrome (ACS) and cerebral arteriosclerosis. Adopting a multicenter, prospective, randomized controlled research methodology, the study targets patients aged 60 and older with ACS and concomitant cerebral atherosclerosis. Of the total sample size of 480 cases, our center will undertake 400, which will be randomly assigned to either the Tanhuo Decoction treatment group or the control group. The study will analyze and compare the two groups in terms of phlegm-heat syndrome scores, inflammatory biomarkers, cardiac function, and the incidence of Major Adverse Cardiac and Cerebrovascular Events (MACCE) during hospitalization and within a one-year post-discharge follow-up period.

Main text

1.Background and Rationale

As China enters an aging society, the coexistence of elderly Coronary Artery Disease (CAD) and cerebrovascular atherosclerotic disease has become increasingly prevalent. These conditions represent different clinical manifestations of a shared underlying pathology—atherosclerosis—within two vital organ systems, which interact and exacerbate one another. Despite receiving standard Western medical interventions, including pharmacotherapy, interventional therapy, carotid endarterectomy, and coronary artery bypass grafting (CABG), patients with comorbid coronary and cerebrovascular diseases continue to face poor prognoses.

As early as the 1960s, Professor Zhao Buchang began researching Traditional Chinese Medicine (TCM) therapies for cardio-cerebrovascular diseases. This approach is rooted in the TCM theories of "treating different diseases with the same method," "common origin of brain and heart," and "brain-heart co-pathology," based on the physiological and pathological connections between the brain and heart. In 1993, Professor Zhao Buchang, along with Professor Wu Haiqin and Dr. Zhao Tao, innovatively proposed the theory of "Simultaneous Treatment of Brain and Heart" . This theory interprets the pathogenesis and therapeutic principles of cardio-cerebrovascular diseases from a holistic perspective, guiding clinical practice with significant efficacy. Subsequent extensive clinical, experimental, and literature research has validated "Simultaneous Treatment of Brain and Heart" as a scientifically rigorous and innovative theoretical framework.

Cardio-cerebrovascular atherosclerosis is a chronic inflammatory disease centered on lipid accumulation. Inflammation remains a critical residual risk even after lipid levels are effectively controlled, and its predictive value for cardiovascular events exceeds that of residual cholesterol risk [1]. Our team’s recent studies have shown that inflammatory mechanisms contribute to atherosclerotic plaque vulnerability [2] and disease severity [3]. While Glucagon-like peptide-1 (GLP-1)

receptor agonists reduce atherosclerosis through anti-inflammatory effects independent of glucose lowering [4], and glutamine intervention exerts protective effects by inhibiting inflammatory signaling pathways [5], landmark clinical trials such as CANTOS [6], COLCOT [7], and LoDoCo2 [8] have provided high-level evidence-based support for the clinical application of anti-inflammatory therapies. However, Western pharmacological interventions for inflammatory pathways face challenges such as single-target limitations, high costs, or significant adverse effects. For instance, IL-1β monoclonal antibodies failed to achieve widespread clinical use due to an increased risk of fatal infections [9]. Currently, only low-dose colchicine (0.5mg/d) is recommended for the secondary prevention of coronary heart disease in the *2023 ESC Guidelines for the Management of Acute Coronary Syndromes* [10].

Due to their advantages in systemic regulation and multi-target modulation of signaling pathways, TCM formulas have recently been found to play a crucial role in reducing inflammatory responses and improving prognosis in CAD [11, 12]. Tanhuo Decoction is an empirical prescription developed by Professor Gao Li and his team at Xuanwu Hospital, Capital Medical University, based on years of clinical practice. Research has confirmed its multi-faceted neuroprotective effects in patients with ischemic stroke [13, 14], and small-sample studies on Tanhuo Decoction intervention in acute myocardial infarction have also demonstrated its cardio-renal protective effects [15]. Based on these preliminary findings, this project aims to establish a research platform and team dedicated to cardio-cerebrovascular atherosclerotic comorbidities in the elderly to verify the efficacy of Tanhuo Decoction in controlling inflammation and improving patient prognosis. Therefore, the implementation of this project is of great clinical significance.

2. Research Objectives

The objective of this study is to evaluate the efficacy of Tanhuo Decoction in managing inflammatory biomarkers among elderly patients with comorbid Acute Coronary Syndrome (ACS) and cerebral atherosclerosis. The specific observational

indices and clinical outcomes include Phlegm-Heat syndrome scores, inflammatory markers, cardiac function, and the incidence of Major Adverse Cardiac and Cerebrovascular Events (MACCE)

3. Research Methods and Design

3.1 Study Design

Using a prospective randomized controlled research methodology, patients meeting the inclusion and exclusion criteria with ACS and concomitant cerebrovascular atherosclerosis will be randomly assigned to either the Tanhuo Decoction treatment group or the control group. The study will analyze and compare the efficacy of Tanhuo Decoction in controlling inflammatory responses.

3.2 Study Population

The study population consists of patients with Acute Coronary Syndrome (ACS) and concomitant cerebral atherosclerosis. ACS includes acute myocardial infarction (AMI) and unstable angina (UA). The diagnostic criteria for AMI include persistent chest pain, ST-segment elevation or depression on electrocardiogram (ECG), and significant elevation of cardiac enzymes (such as troponin), following the exclusion of other etiologies. The diagnostic criteria for UA include chest pain and ST-segment elevation or depression on ECG, with negative cardiac enzymes (such as troponin), following the exclusion of other etiologies. Cerebral atherosclerosis is diagnosed based on carotid intima-media thickening (IMT $\geq$ 1.0 mm).

The study population will be recruited from cardiology departments across multiple centers, including Xuanwu Hospital of Capital Medical University, Beijing Friendship Hospital of Capital Medical University, Peking University First Hospital, Beijing Huimin Hospital, Beijing Electric Power Hospital, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Xiyuan Hospital of China Academy of Chinese Medical Sciences, and Dongfang Hospital of Beijing University of Chinese Medicine, from September 2025 to December 2028.

3.3 Selection Criteria

Inclusion Criteria: (1) Hemodynamic stability achieved within 24 hours of

treatment for Acute Coronary Syndrome; (2) A confirmed diagnosis of previous ischemic cerebrovascular disease, or intracranial or extracranial arterial stenosis 50% or greater confirmed by carotid and cerebral ultrasound after admission; (3) Presence of Phlegm-Heat syndrome: assessment includes tongue body, tongue coating, bowel movements, mental state, facial expression, respiration, fever, pulse, oral sensation, and urine, with a total weighted score of 7 or higher; (4) Age 60 years or older; (5) Male or female; (6) Signed informed consent.

Exclusion Criteria: (1) Hemodynamic instability persisting beyond 24 hours, ACS-related hypotension (blood pressure below 90/60 mmHg), or patients requiring coronary artery bypass grafting (CABG) based on coronary anatomy; (2) Pre-existing chronic heart failure of any etiology; (3) History of ischemic stroke, peptic ulcer, active bleeding, or major surgery within the past 3 months; (4) Hepatic or renal insufficiency: ALT or AST greater than 5 times the upper limit of normal, or creatinine clearance less than 30 mL/min/1.73m2; (5) History of bronchial asthma; (6) Platelet count less than 80x10^9/L or anemia (hemoglobin 100 g/L or less); (7) Contraindication or allergy to aspirin, clopidogrel, ticagrelor, or statins; (8) History of neoplastic diseases; (9) Known allergy to components of the Traditional Chinese Medicine decoction.

Withdrawal Criteria: (1) Participant withdraws informed consent or is lost to follow-up; (2) Changes or progression in clinical condition where the investigator determines that continued participation poses an increased risk; (3) Pregnancy in female participants; (4) Serious or intolerable adverse events that preclude continued participation; (5) Concurrent participation in other clinical trials during the study period; (6) Poor compliance, where the investigator determines the participant is unsuitable to continue after a comprehensive evaluation.

3.4 Intervention and Control Group Design

Patients with elderly acute coronary syndrome combined with cerebral atherosclerosis who meet the inclusion and exclusion criteria will be randomly assigned to either the Tanhuo Decoction treatment group or the control group in a 1:1 ratio. The control group will receive a placebo.

Treatment Group: Tanhuo Decoction, one bag per dose, twice daily, administered orally for a total of 7 days.

3.5 Investigational Products

Tanhuo Decoction is currently an in-hospital Traditional Chinese Medicine (TCM) preparation of Xuanwu Hospital, Capital Medical University. Its composition includes: Forsythiae Fructus (Lianqiao) 10g, Coptidis Rhizoma (Huanglian) 9g, Lophatheri Herba (Danzhuye) 9g, Arisaema cum Bile (Dannanxing) 9g, and Rhei Radix et Rhizoma (Dahuang) 5g. The dosage is one dose per day. The hospital's Pharmacy Department prepares the decoction through water decocting and concentration to obtain 200 mL of decoction, which is then packaged in bags and delivered to the wards. It is stored in a refrigerator at 4°C, and 100 mL is administered warm twice daily (morning and evening) via oral intake or nasal feeding. Years of clinical application have demonstrated that Tanhuo Decoction has an excellent safety profile, with no adverse reactions reported to date. This multi-center study uses Tanhuo Decoction exclusively supplied by the Department of Pharmacy of Xuanwu Hospital, Capital Medical University.

3.6 Concomitant Medications and Precautions

Tanhuo Decoction should be administered at least 30 minutes apart from other medications. There are no known drug-drug contraindications (incompatibility).

3.7 Randomization Design

In this study, a random number table will be generated using SAS 9.4 software, and patients will be assigned to two groups based on the randomization results.

3.8 Selection and Validation of Primary Outcome Measures

Primary Endpoints: The primary evaluation includes comparing changes in white blood cell (WBC) count, neutrophil count, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) levels between 7 days of treatment and 1 month post-discharge. Additionally, differences in Phlegm-Heat syndrome scores and multi-omics results will be assessed between the two groups after 7 days of treatment, alongside changes in left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) at 1 month and 1 year post-discharge. Secondary

Endpoints: The secondary evaluation focuses on the 12-month incidence of major adverse cardiac and cerebrovascular events (MACCE) following discharge, including cardiovascular death, non-fatal myocardial infarction, stent thrombosis, ischemia-driven revascularization, stable or unstable angina, heart failure, transient ischemic attack (TIA), and cerebral infarction. Safety Endpoints: Safety will be monitored based on the incidence of all adverse events (AEs) during the administration of Tanhuo Decoction and the incidence of serious adverse events (SAEs)

3.9 Follow-up Plan

All patients will undergo follow-up at 1 month, 3 months, 6 months, and 12 months after discharge.

4. Preliminary Research Foundation

As an in-hospital preparation, Tanhuo Decoction has become a synergistic formula for acute cerebral infarction, supported by numerous published original articles and authorized patents. It has been confirmed that Tanhuo Decoction significantly improves the prognosis and cerebral perfusion of patients with acute cerebral infarction (Phlegm-Heat syndrome), while reducing serum inflammatory factor levels, inhibiting inflammatory responses, and regulating gut microbiota. Furthermore, network pharmacology research indicates that Coptidis Rhizoma (Huanglian), Rhei Radix et Rhizoma (Dahuang), and Lophatheri Herba (Danzhuye) exert anti-inflammatory and antioxidant effects through multiple signaling pathways.

5.Research Site and Data Management

After sample collection, specimens will be sent to the Department of Clinical Laboratory of our hospital. A standardized Case Report Form (CRF) and database will be established. Strict supervision will be implemented throughout the processes of data reception and entry, data verification, data auditing, database locking, data export and transmission, as well as the archiving of data and data management documents.

6. Statistical Analysis Plan

6.1 Sample Size Calculation

Sample Size Calculation for Patients with Acute Coronary Syndrome and Coexisting Cerebrovascular Atherosclerosis in the Department of Cardiology:This study is a prospective, randomized controlled trial employing a 1:1 parallel-group design. The changes in white blood cell (WBC) count, neutrophil count, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) levels were selected as the primary endpoints. With a significance level (α) set at 0.05 (two-tailed) and a statistical power (1-β) of 85%, the required sample sizes per group for each indicator were calculated as follows: 119 cases for WBC and neutrophil counts, 86 cases for IL-6, and 191 cases for hs-CRP. Accounting for a 20% dropout rate, the adjusted sample sizes for each indicator are: 149 cases for WBC and neutrophil counts, 108 cases for IL-6, and 239 cases for hs-CRP. Based on these calculations and a conservative estimate using the maximum sample size required for hs-CRP, each group should enroll 239 cases, resulting in a total required sample size of 478. Considering clinical feasibility, this study finally intends to include a total of 480 eligible patients.

6.2 Statistical Analysis Methods

All statistical tests will be two-tailed, and a P-value < 0.05 will be considered statistically significant (unless otherwise specified). Quantitative indicators will be described using mean, standard deviation, median, minimum, maximum, and interquartile range (Q1, Q3), while categorical indicators will be described using frequencies and percentages. Group comparisons will employ the independent samples t-test (for normally distributed data with homogeneity of variance) or the Wilcoxon rank-sum test for quantitative data, the Chi-square test or Fisher's exact test for categorical data, and the Wilcoxon rank-sum test or CMH test for ordinal data. Enrollment and baseline characteristics, including demographic data, medical history, and dropout reasons, will be analyzed using the Full Analysis Set (FAS) to ensure group comparability. For primary efficacy endpoints (inflammatory markers), a superiority (non-inferiority/equivalence) design will be utilized with a hypothesis of H_0: $P_{treatment} - P_{control} \geqslant 0$, H_1: $P_{treatment} - P_{control} < 0$, and $\alpha = 0.025$ (one-tailed), evaluated using both FAS and the Per-Protocol Set (PPS). Secondary efficacy endpoints will be

analyzed based on general statistical principles using FAS and PPS, while safety analysis will be performed on the Safety Set (SS) through descriptive statistics. Missing data will be handled according to the pre-specified Statistical Analysis Plan (SAP) finalized before database lock, with primary efficacy data utilizing the most conservative imputation methods. The analysis populations are defined as follows: the FAS includes all randomized participants who received treatment based on the Intention-To-Treat (ITT) principle; the PPS includes those who strictly adhered to the protocol and completed all required assessments; and the SS includes all randomized patients who received at least one dose of study medication and underwent at least one safety evaluation.

7. Recording and Reporting of Adverse Events

(I) Definitions: An Adverse Event (AE) is defined as any untoward medical occurrence in a study participant after receiving the study product, including symptoms, signs, diseases, or abnormal laboratory findings, which does not necessarily have a direct causal relationship with the treatment. A Serious Adverse Event (SAE) refers to any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or loss of function, or is a congenital anomaly or birth defect. An Adverse Drug Reaction (ADR) refers to any harmful and unintended response where a causal relationship between the study product and the event is at least a reasonable possibility. (II) Assessment of Severity: Severity is a qualitative evaluation of the intensity of the event and does not necessarily reflect its clinical seriousness or relationship to the study drug. Grading will be based on the NCI CTCAE 5.0 (Grade 1 to 5); if these criteria are inapplicable, the investigator’s clinical judgment shall prevail. (III) Assessment of Causality: The relationship between the AE and the study product will be categorized into five levels: Definitely Related, Probably Related, Possibly Related, Possibly Unrelated, or Definitely Unrelated. (IV) Recording: The investigator and designated personnel are responsible for identifying, confirming, and recording all AEs and SAEs. (V)

Reporting of SAEs: Any SAE, regardless of its relationship to the intervention, must be reported to the Ethics Committee within 24 hours of awareness. (VI) Follow-up: Following the initial report, investigators must proactively follow up on all AEs/SAEs during subsequent contacts until the event is resolved, stabilized, otherwise explained, or the participant withdraws from the study.

8. Ethical and Regulatory Considerations

This study will be conducted in strict accordance with the Declaration of Helsinki and all relevant international and domestic policies and regulations. Investigators and research personnel must be familiar with and strictly adhere to the study protocol while pre-establishing and executing effective risk prevention and control measures. Prior to implementation, the study protocol, informed consent forms, and other necessary documents must be submitted to and approved by the Institutional Review Board (IRB). Furthermore, the study will be registered with the Medical Research Registration and Filing Information System of the National Health Commission to ensure compliance and transparency. For approved studies, investigators are required to submit timely reports regarding study progress, serious adverse events (SAEs), protocol deviations, suspensions, terminations, and study completion. Regarding the Informed Consent Process, a structured plan must be established to define who, when, where, and how consent is obtained. Specifically: 1) Personnel obtaining consent must be appropriately qualified and ensure sufficient time is allocated for the process; 2) The location for obtaining consent must ensure participant privacy; 3) Consent must be obtained from the participant personally or their legal guardian; 4) The method of consent (written, electronic remote, or telephonic) must be specified, and if remote methods are used, rigorous procedures for recording and archiving process documentation must be implemented.

9. Study Management

(I) Protocol Amendments: Any modifications to the approved protocol, informed consent forms, recruitment materials, or other participant-facing documents must be submitted to the Ethics Committee (EC) as "Amendments" for review. All revisions, whether major or minor, must be documented in writing; substantial amendments affecting participant safety, study scope, or scientific quality require formal EC approval. Emergencies requiring immediate protocol deviations to eliminate hazards to participants may be implemented instantly but must be reported to the EC as soon as possible. Minor administrative changes, such as updates to contact information or study centers, do not require formal approval but must be filed with the EC for record-keeping. (II) Quality Control: Designated personnel will perform quality control (QC) throughout the study, ensuring that: 1) formal EC approval and regulatory filings are obtained prior to implementation; 2) all researchers receive standardized training to ensure uniform recording and judgment criteria; 3) enrolled participants strictly meet all inclusion and exclusion criteria; 4) Case Report Forms (CRFs) are filled out accurately and authentically; 5) all observations and findings are verified to ensure data reliability and traceability; and 6) all SAEs and major protocol deviations are reported to the EC promptly. (III) Premature Termination: The study may be terminated prematurely if: 1) serious safety concerns are identified; 2) the study drug demonstrates insufficient efficacy or lack of clinical value; 3) significant design flaws or severe protocol deviations (e.g., violations of randomization or medication protocols) render the assessment of drug effects impossible; or 4) regulatory authorities mandate the termination of the research.

10. Research Implementation Conditions

Capital Medical University Xuanwu Hospital provides full support for this study, including the necessary research premises, equipment, and facilities required to fulfill the research tasks. The Principal Investigator and the research team possess the requisite qualifications, professional expertise, experience, and technical capabilities essential for the study. Furthermore, team members hold appropriate medical practice

qualifications and extensive clinical experience, ensuring the safety and medical care of study participants. All designated team members are qualified or have been specifically trained to handle the informed consent process and remain available to address any inquiries regarding safety issues at any time.

11. References

[1] Ridker PM, Bhatt DL, Pradhan AD, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. Lancet. 2023. 401(10384): 1293-1301.

[2] Li Q, Leng K, Liu Y, et al. The impact of hyperglycaemia on PKM2-mediated NLRP3 inflammasome/stress granule signalling in macrophages and its correlation with plaque vulnerability: an in vivo and in vitro study. Metabolism. 2020. 107: 154231.

[3] Li Q, Liu Y, Xia X, et al. Activation of macrophage TBK1-HIF-1α-mediated IL-17/IL-10 signaling by hyperglycemia aggravates the complexity of coronary atherosclerosis: An in vivo and in vitro study. FASEB J. 2021. 35(5): e21609.

[4] Xia J, Li Q, Liu Y, et al. A GLP-1 Analog Liraglutide Reduces Intimal Hyperplasia After Coronary Stent Implantation via Regulation of Glycemic Variability and NLRP3 Inflammasome/IL-10 Signaling in Diabetic Swine. Front Pharmacol. 2020. 11: 372.

[5] Zhang H, Wang C, Sun H, et al. Glutamine supplementation alleviated aortic atherosclerosis in mice model and in vitro. Proteomics. 2024. 24(5): e2300179.

[6] Maffia P, Guzik TJ. When, where, and how to target vascular inflammation in the post-CANTOS era. Eur Heart J. 2019. 40(30): 2492-2494.

[7] Roubille F, Bouabdallaoui N, Kouz S, et al. Low-Dose Colchicine in Patients With Type 2 Diabetes and Recent Myocardial Infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Diabetes Care. 2024. 47(3): 467-470.

[8] Opstal T, van Broekhoven A, Fiolet A, et al. Long-Term Efficacy of Colchicine in Patients With Chronic Coronary Disease: Insights From LoDoCo2. Circulation. 2022.

145(8): 626-628.

[9] Matter MA, Paneni F, Libby P, et al. Inflammation in acute myocardial infarction: the good, the bad and the ugly. Eur Heart J. 2024. 45(2): 89-103.

[10]Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023. 44(38): 3720-3826.

[11]Yang Y, Li X, Chen G, et al. Traditional Chinese Medicine Compound (Tongxinluo) and Clinical Outcomes of Patients With Acute Myocardial Infarction: The CTS-AMI Randomized Clinical Trial. JAMA. 2023. 330(16): 1534-1545.

[12]Ge JB, Fan WH, Zhou JM, et al. Efficacy and safety of Shexiang Baoxin pill (MUSKARDIA) in patients with stable coronary artery disease: a multicenter, double-blind, placebo-controlled phase IV randomized clinical trial. Chin Med J (Engl). 2021. 134(2): 185-192.

[13]Guo Q, Ni C, Li L, et al. Integrated Traditional Chinese Medicine Improves Functional Outcome in Acute Ischemic Stroke: From Clinic to Mechanism Exploration With Gut Microbiota. Front Cell Infect Microbiol. 2022. 12: 827129.

[14]李明聪, 赵婷, 赵晖等. 痰火方改善脑缺血大鼠脑灌注及保护神经胶质细胞的作用. 北京中医药大学学报 2021年44卷7期 605-614页 ISTIC PKU CSCD CA. 2021：北京市科学技术委员会"十病十药"研发专项.

[15]Guo C, Zhang T, He L, et al. Cardiorenal protective effects of Tanhuo decoction in acute myocardial infarction via regulating multi-target inflammation and metabolic signaling pathways. Front Pharmacol. 2025. 16: 1555605.