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Efficacy and safety of safflower yellow for injection in acute ischemic stroke: A Meta-analysis

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Chen, ZG[1]; Chen, LL[2]; Ye, QM[3]; Xuan, JW[4]; Bing, ST[5].

Corresponding author:
Zheng-guo Chen

854719218@qq.com

Author Affiliation:
Department of Clinical Research Management Office, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou 510150, China.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 September 2023 and was last updated on 06 September 2023.

INTRODUCTION

Review question / Objective The purpose of our study is to analyze the efficacy and safety outcomes of using safflower yellow for injection combined with conventional treatment versus conventional treatment in the treatment of patients with acute ischemic stroke. The types of studies included in the systematic review are limited to randomized controlled trials test.

Rationale According to the PICOS principle, strict standards for literature inclusion and sorting were formulated. Two researchers conducted literature screening, data extraction and cross-checking according to pre-set standards. NoteExpress software was used for document management, and the primary screening was performed by reading the titles and abstracts of the documents after duplicate checking, and the full-text re-screening of potential documents that met the criteria was carried out.S tatistical analyses were performed using the statistical software R-4.3.1.Meta-analysis was conducted when a minimum of three studies reported pertinent outcomes. For dichotomous outcomes, the relative risk (RR) with 95% confidence interval (CI) was computed. For continuous outcomes, either the mean difference (MD) or the standardized mean difference (SMD), along with their respective 95% CIs, were calculated.

Condition being studied At present, the approach to treating acute ischemic stroke (AIS) involves multiple strategies, such as thrombolysis, intervention, anti-platelet therapy, anticoagulation, lowering of fibrinogen and blood lipid levels, expansion of blood capacity, and neuroprotection. It's important to highlight that ultra-early thrombolysis stands out as the most potent

treatment.Nevertheless, the strict treatment time window for thrombolysis imposes significant limitations on its application in China, resulting in a restricted pool of eligible patients.
Consequently , the need arises to explore alternate effective therapeutic methods. Traditional Chinese medicine (TCM) holds several advantages, encompassing diverse targets, effective synergy, and minimal side effects, thus being extensively employed in managing complex illnesses.The constituent of Safflower Yellow Injection is Safflower Yellow, hydroxysafflor yellow A is a major component of Safflower Yellow. The protective effect of hydroxysafflor yellow A in ischemic stroke has been investigated in previous studies, which have shown effects of antithrombosis, anticoagulation, antioxidation, anti-inflammation, and anticalcium dysregulation.

METHODS

Search strategy A systematic search was conducted across multiple databases including PubMed, Web of Science, Cochrane Library, EMBASE, CNKI (China National Knowledge Infrastructure), China Biomedical Literature Service System (SinoMed), Wanfang database, and Weipu database. The search encompassed records from inception until June 2023, without any language restrictions. The Medical Subject Heading (MeSH) terms and free-text keywords were utilized, including "Acute ischemic stroke," "Ischemic Stroke," "Stroke," "Acute Cerebral Infarction," "Cerebral Infarction," "Brain Infarction," ” Safflower Yellow.”

Participant or population All cases included in the study were diagnosed with acute ischemic stroke (AIS). The recruitment exclusively focused on patients who experienced onset within a span of 2 weeks. No limitations were imposed regarding age, gender, race, or disease severity.

Intervention The experimental groups were administered a combination of Safflower Yellow for Injection (SYI) along with conventional medical treatment. Co-interventions were allowed if they were offered equally to each study arm. However, trials incorporating additional Chinese herbal medicines, whether in the treatment or control groups, were excluded from consideration.

Comparator The control group exclusively underwent conventional medical treatment, which encompassed interventions such as anti-platelet aggregation, anticoagulation, lipid-lowering, correction of water and electrolyte disorders, correction of acid-base imbalance, enhancement of cerebral circulation, and utilization of neuroprotective agents.There were no limitations on the dosage and duration of the treatment. Co-interventions were allowed if they were offered equally to each study arm. However, trials incorporating additional Chinese herbal medicines, whether in the treatment or control groups, were excluded from consideration.

Study designs to be included Studies designed as randomized controlled trials (RCTs) were included, with no limitations imposed on factors such as language, geographical location, publication date, or study phase.

Eligibility criteria Studies that met one of the following conditions were excluded: 1. Duplicate publications; 2. Incomplete literature (such as no mention of treatment plans for the experimental group and control group, lack of the above measurable outcome indicators, etc.); 3. Unavailable Full text; 4. Trials involving other traditional Chinese medicines used in the trial group were excluded.

Information sources Computer searches were conducted on CNKI, Wanfang Database, VIP.com, Chinese Biomedical Literature Database, PubMed, Embase, Web of Science and Cochrane Library.

Main outcome(s) The primary outcome encompassed the clinical effectiveness rate, the National Institutes of Health Stroke Scale (NIHSS) scores, and adverse reactions (ADRs). The clinical effectiveness rate defined according to the nationally approved criteria. We considered treatment failures as instances where there was no improvement (with a decrease of 18%~45% in function defect score), deterioration (with a decrease of about 17% in function defect score), or death.
The secondary outcomes included the Barthel Index scores, hemorheological indexes (hematocrit (HCT), plasma viscosity (PV), fibrinogen (FIB) levels), serum nitric oxide (NO) levels, and serum inflammatory markers (interleukin-6 (IL-6) and interleukin-8 (IL-8)).

Data management Two authors (ZG Chen and LL Chen) conducted a separate examination of the titles and abstracts to identify trials that could potentially meet the eligibility criteria.Subsequently, they thoroughly reviewed the full texts to determine trials that met the eligibility criteria. We proceeded to extract pertinent information from the included trials, encompassing details of the first authors and year of publication, randomization protocols, participant characteristics (including age, gender,

and clinical stage), sample size, descriptions of interventions and controls, as well as outcome measures.The discrepancies were resolved through consensus and if required, they were further adjudicated by the third author (QM Ye).

Quality assessment / Risk of bias analysis Using the risk of bias tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions, the methodological quality of RCTs was independently evaluated by two authors (ZG Chen and LL Chen). In case of any discrepancies, resolution was achieved through consultation with the third author (QM Ye). The following items were assessed: (1) selection bias: random sequence generation, allocation concealment; (2) performance bias: blinding of participants and personnel; (3) detection bias: blinding of outcome assessment; (4) attrition bias: incomplete outcome data; (5) reporting bias: selective reporting; (6) other biases.

Strategy of data synthesis S tatistical analyses were performed using the statistical software R-4.3.1.Meta-analysis was conducted when a minimum of three studies reported pertinent outcomes. For dichotomous outcomes, the relative risk (RR) with 95% confidence interval (CI) was computed. For continuous outcomes, either the mean difference (MD) or the standardized mean difference (SMD), along with their respective 95% CIs, were calculated. The heterogeneity among studies was evaluated using the Q test and I2 statistics. If Pheterogeneity≤0.10 or I2>50% (heterogeneity existing), the random-effects model was employed to compute the pooled effect size. Otherwise, the fixed-effects model (also called common-effect model)was utilized.

Subgroup analysis Subgroup analysis was conducted based on the dosage of safflower yellow, whether joint intervention was performed, the severity of the patient's condition, the patient's age at enrollment, and the patient's enrollment time.

Sensitivity analysis We intended to conduct a sensitivity analysis to assess the robustness of the outcomes by excluding studies with uncertain random sequence generation.

Language restriction Chinese and English.

Country(ies) involved China (Department of Clinical Research Management Office, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou 510150, China).

Keywords Safflower yellow; Acute ischemic stroke; Efficacy; Safety; Meta-analysis.

Contributions of each author

Author 1 - Zheng-guo Chen.
Email: 854719218@qq.com
Author 2 - Luan-luan Chen.
Email: luanluanchen@126.com
Author 3 - Qiu-mian YE.
Email: yeqiumiam9006@163.com
Author 4 - Jian-wei Xuan.
Email: jwx02467@gmail.com
Author 5 - Si-Tu Bing.
Email: lilyst@126.com