INPLASY PROTOCOL

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None declared.

Comparative Efficacy and Safety of Panax Notoginseng preparations for Acute Ischemic Stroke: a Bayesian Network Meta-Analysis of Randomized Controlled Trials

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Review question / Objective: **We conducted this Bayesian network meta-analysis (NMA) to identify the differences in efficacy and safety of various panax notoginseng preparations, and prescribe the optimal injections for decision-making.**
Information sources: **We searched the China National Knowledge Infrastructure Database (CNKI), the Chinese Scientific Journals Full-text Database (VIP), the Wan-Fang Database, the Cochrane Library, PubMed, Web of Science and Embase from database inception to September 31, 2022. The free-text keywords and MESH (Medical Subject Heading) terms were utilized. Additionally, the references of related literatures were manually searched to identify further studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 October 2022 and was last updated on 23 October 2022 (registration number INPLASY2022100089).

INTRODUCTION

Review question / Objective: **We conducted this Bayesian network meta-analysis (NMA) to identify the differences in efficacy and safety of various panax notoginseng preparations, and prescribe the optimal injections for decision-making.**

Condition being studied: **Stroke is the second leading cause of motality and third most common cause of disability among people worldwide(Feigin et al., 2021), both treatment and rehabilitation for which imposes a substantial economic cost and leads to severe nursing and financial burdens to patients and families. Ischemic**

stroke (IS) is the most prevalent of the two major stroke types, characterized by localized ischemic necrosis or softening of brain tissues caused by cerebral blood flow impairment or hypoxia, accounting for nearly 70% of all stroke cases(Wang et al., 2017). The foremost therapeutic regimen is to salvage the ischemic penumbra through revascularization including intravenous thrombolysis(IVT) and endovascular treatment(EVT) within a specified time window in patients with non-minor AIS(Tissue Plasminogen Activator for Acute Ischemic Stroke, 1995; Broderick et al., 2013).Unfortunately, the population benefit from IVT has been limited by uncertain onset time, narrow thrombolytic time window, in-hospital delays and increased risk of hemorrhagic transformation(Saver, 2006; Lyden, 2008; Meretoja et al., 2014). Additionally, despite the dual antiplatelet therapy(DAPT) could reduce the risk of stroke among patients with acute minor stroke or transient ischemic attack(TIA) in short term(Wang et al., 2013), the characteristics associated with antiplatelet agents including liver and kidney damage, gastrointestinal reactions(Shimada et al., 2015), increased risk of bleeding ,aspirin resistance(AR)(Hankey and Eikelboom, 2006), polymorphisms of the CYP2C19 gene(Wang et al., 2016b) lead to restrictions in their safe and broad clinical applications for the long term. As such, exploring and developing safe and effective therapies for stroke medication optimization is of significant clinical implication.

METHODS

Participant or population: Patients diagnosed with AIS (within 14 days of onset) defined by the World Health Organization criteria (Hatano, 1976), with computed tomography (CT) or magnetic resonance imaging (MRI) scanning to exclude haemorrhagic stroke. Regardless of age, gender, race or disease severity.

Intervention: The experiment group was treated with western medicine (WM) combined with Panax notoginseng preparations(PNPs), including Xuesaitong injection (XSATI), Xueshuantong injection (XSHTI), Xuesaitong oral agents (XSATO), Xueshuantong oral agents(XSHTO) and Sanqi Tongshu oral agents(SQTSO) regardless of dosage and duration of treatment.

Comparator: Patients in the control group were both received WM with or without placebo of PNPs or WM plus another PNPs. According to the guidelines (Peng et al, 2018), the commonly used WM were primarily including antihypertensive, hypoglycemic, hypolipidemic, anti-platelet aggregation, improving brain tissue, nutritional brain cells, etc.

Study designs to be included: We included randomised controlled trials (RCTs) regardless of blinding, publication status, or language.

Eligibility criteria: Eligibility Criteria Types of studiesWe included randomised controlled trials (RCTs) regardless of blinding, publication status, or language.Types of participantsPatients diagnosed with AIS (within 14 days of onset) defined by the World Health Organization criteria (Hatano, 1976), with computed tomography (CT) or magnetic resonance imaging (MRI) scanning to exclude haemorrhagic stroke. Regardless of age, gender, race or disease severity. Types of interventionsThe experiment group was treated with western medicine (WM) combined with Panax notoginseng preparations(PNPs), including Xuesaitong injection (XSATI), Xueshuantong injection (XSHTI), Xuesaitong oral agents (XSATO), Xueshuantong oral agents(XSHTO) and Sanqi Tongshu oral agents(SQTSO) regardless of dosage and duration of treatment. Patients in the control group were both received WM with or without placebo of PNPs or WM plus another PNPs. According to the guidelines (Peng et al, 2018), the commonly used WM were primarily including antihypertensive, hypoglycemic, hypolipidemic, anti-platelet aggregation, improving brain tissue, nutritional brain cells, etc.Types of outcomesThe primary outcome was the death or dependency at the end of long-

term follow-up or the scheduled follow-up. We defined dependency as dependent on others in activities of daily living - for example, the Barthel Index score of 60 or less, the modified Rankin Scale graded 3 to 5 (Sulter 1999), or the physicians'own definition.Additionally, the secondary outcomes included: (1) The total effective rate, the change in neurological function deficit assessed by validated scales such as the National Institute of Health Stroke Scale (NIHSS) or the nationally approved Neurological Function Deficit Score (NFDS), defined as the improvement in neurological deficit after treatment. According to the nationally approved criteria, we regarded the effective number as the sum of cured, significant and effective people (function defect score decreased by 18%–100%). (2) Neurological function deficit score assessed by NIHSS after treatment. (3) Activities of daily living function assessed by BI after treatment. (4) The proportion of adverse events (AEs).Exclusion CriteriaWe excluded studies that met the following criteria: (1) Animal experiment, reviews, meta-analyses, retrospective studies or case reports. (2) Research data had serious errors or did not have access to the full text after seeking help online or contacting the corresponding author through email. (3) Repeated publication retained the first published article. (4) Studies with incomparable baseline data between the two groups. (5) Studies with a high risk of bias in sequence generation according to the Cochrane Collaboration's risk of bias tool. (6) The interventions were combined with thrombolytic therapy or other Chinese herbal medicines or common technology of TCM, such as acupuncture, moxibustion and massage, etc. (7) The number of cases was less than 60.(8)Studies with only one author.

Information sources: We searched the China National Knowledge Infrastructure Database (CNKI), the Chinese Scientific Journals Full-text Database (VIP), the Wan-Fang Database, the Cochrane Library, PubMed, Web of Science and Embase from database inception to September 31, 2022. The free-text keywords and MESH (Medical Subject Heading) terms were utilized. Additionally, the references of related literatures were manually searched to identify further studies.

Main outcome(s): The primary outcome was the death or dependency at the end of long-term follow-up or the scheduled follow-up. We defined dependency as dependent on others in activities of daily living - for example, the Barthel Index score of 60 or less, the modified Rankin Scale graded 3 to 5 (Sulter 1999), or the physicians'own definition.

Additional outcome(s): Additionally, the secondary outcomes included: (1) The total effective rate, the change in neurological function deficit assessed by validated scales such as the National Institute of Health Stroke Scale (NIHSS) or the nationally approved Neurological Function Deficit Score (NFDS), defined as the improvement in neurological deficit after treatment. According to the nationally approved criteria, we regarded the effective number as the sum of cured, significant and effective people (function defect score decreased by 18%–100%). (2) Neurological function deficit score assessed by NIHSS after treatment. (3) Activities of daily living function assessed by BI after treatment. (4) The proportion of adverse events (AEs).

Data management: One review author (XL Xie) imported the bibliographic records retrieved by electronic searches into NoteExpress 3.2 and excluded duplicate and obviously irrelevant studies. We obtained the full text of the remaining studies, and two review authors (XY Zheng and XY Shi) independently assessed these according to the predefined eligibility and exclusion criteria. We resolved any disagreements by discussion and, if necessary, in consultation with a third author (TT Li).
We extracted data by using Microsoft Excel (Microsoft Corp, Redmond, WA,USA) from the included studies as follows: (1) Information of the studies including author names, title and publication data; (2) Characteristics of Patients including sample sizes, age, gender, and onset time; (3) Intervention including the types of

PNPs, dosages, frequency and duration; (4) Primary and secondary outcomes including the clinical effectiveness rate, NIHSS score, BI score, and adverse events.

Quality assessment / Risk of bias analysis: Two review authors (HR Zhang and QY Jia) evaluated and cross-checked independently the methodological quality of included studies according to the Cochrane Risk of Bias tool(Higgins et al., 2011), including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other possible biases. Each item was classified into "low risk", "high risk" and "unclear risk".. Differences were discussed, and a third author (XL Xie) was contacted if consensus was not reached.

Strategy of data synthesis: The NMA was performed by Stata12.0 software and GeMTC package of R software. A Bayesian hierarchical random-effects model was used to conduct NMAs according to Markov Chain Monte Carlo algorithm(Bodnar et al., 2017). For dichotomous variables, the results were presented as odds ratios(ORs) or relative risk(RR)with 95% confidence intervals (95% CIs). For continuous variables, the results were presented as the mean differences(MDs) with 95% CIs. If the range of 95% CIs of ORs or RRs did not across 1 and 95% CIs of MDs did not across 0, the differences between the groups would be considered statistically significant. The model was run with four chains and 50,000 iterations, discarding the initial 20,000 iterations as burn-in for annealing to eliminate the influence of the initial value(Crainiceanu and Goldsmith, 2010).The surface under the cumulative ranking curve (SUCRA) was performed to rank the probabilities for different interventions of each outcome(Salanti et al., 2011). The node-splitting analysis was employed to split mixed evidence into direct evidence and indirect evidence to evaluate the consistency of the model. The multi-dimensional efficacy analysis was performed to integrate the results of multiple outcomes to obtain the optimal intervention. Furthermore, the publication bias of included RCTs were detected though a comparison adjusted funnel plot(Chaimani et al., 2013).

Subgroup analysis: When P < 0.1 and I2 was > 50%, we explored the sources of heterogeneity using a subgroup analysis.

Sensitivity analysis: When the heterogeneity was high, we performed a sensitivity analysis to find the influence of every study on the heterogeneity, a single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs.

Country(ies) involved: All authors/ China.

Keywords: acute ischemic stroke, panax notoginseng preparation, randomized controlled trial, network meta-analysis, bayesian model.

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