INPLASY PROTOCOL

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None declared.

Constructing evidence for the treatment of cerebral ischemia-reperfusion injury with ligustrazine: a preclinical meta-analysis

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Review question / Objective: (1) Population (P): rat or mouse model, cerebral ischemia-reperfusion injury model was successfully established. (2) Intervention (I): ligustrazine was used to treat cerebral ischemia-reperfusion injury by injection or gavage. (3) Comparison (C): cerebral ischemia-reperfusion injury model rats or mice without ligustrazine treatment or receiving the same amount of saline, etc. (4) Outcome (O): to evaluate the protective/therapeutic effects of ligustrazine on cerebral ischemia-reperfusion injury, including neurological recovery, infarct volume, cerebral edema, etc.

Eligibility criteria: (1) Population (P): the target disease was not ischemic stroke, or the animal species were not rats or mice. (2) Intervention (I): the drugs used in the study were not ligustrazine, including mixed solution, combination with other drugs, etc. (3) Comparison (C): the control group was a non-blank control. Or another drug of unknown efficacy was used. (4) Outcome (O): the article did not report the relevant outcome indicators or the relevant data could not be obtained. (5) Study design (S): the types of articles are methodological research and non-original research, including review articles, reviews, conference reports,etc.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 June 2023 and was last updated on 01 June 2023 (registration number INPLASY202360002).

INTRODUCTION

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cerebral ischemia-reperfusion injury, including neurological recovery, infarct volume, cerebral edema, etc.

Condition being studied: Traditional Chinese Medicine (TCM) has certain advantages in multi-site and multi-target comprehensive treatment and overall regulation. Ligustrazine (2,3,5,6-tetramethylpyrazine), the main active ingredient of Chuanxiong, is a traditional Chinese medicine. It has been widely used in the treatment of ischemic cardiovascular and cerebrovascular diseases, such as atherosclerosis, hypertension and stroke, due to its functions of activating blood, qi and removing blood stasis. It has a good effect on the prevention and treatment of ischemic cerebrovascular diseases. Ligustrazine is an alkaloid monomer isolated from Ligusticum Chuanxiong with the molecular formula of $C_8H_{12}N_2$. The therapeutic effect of ligustrazine on ischemic brain diseases has been clinically and experimentally validated. However, the mechanism and optimal dose-time of tetramethylpyrazine in the treatment of cerebral ischemia-reperfusion injury are still unclear. This study aims to elaborate its mechanism of action by combining with relevant articles, and to clarify the optimal dose and time of tetramethylpyrazine in the treatment of cerebral ischemia-reperfusion injury.

METHODS

Search strategy: #1 "ligustrazine" OR"tetramethylpyrazine"OR"tetramethylpyrazine hydrochloride"OR "Liqustrazine"OR"TMPZ"OR "tetramethylpyrazine nitrone"OR "chuanxiongzine"OR"3-hydro-2,2,5,6-tetramethylpyrazine"OR"tetramethylpyrazine diphenylmethylpiperazidine"OR"3,5,6-trimethylpyrazinecarboxylic acid" OR"C8H12N2"OR"2,3,5,6-Tetramethylpyrazine"OR"2,3,5,6-Tetramethyl"
#2 "Cerebral Infarction"OR"Acute Ischemic Stroke"OR"Cerebral Infarct"OR"Infarction, Cerebral"OR"Infarctions, Cerebral"OR"Cerebral Infarct" "Cerebral Infarcts"OR"Ischemic Stroke"OR "MCAO"

OR "OGD/R"OR"cerebral ischemia reperfusion injury"
#3 #1 AND #2.

Participant or population: Rat or mouse model, cerebral ischemia-reperfusion injury model was successfully establishedrat experiments and mouse experiments.

Intervention: Ligustrazine was used to treat cerebral ischemia-reperfusion injury by injection or gavage.

Comparator: Cerebral ischemia-reperfusion injury model rats or mice without ligustrazine treatment or receiving the same amount of saline, etc.

Study designs to be included: Original article evaluating the protective/therapeutic effects of ligustrazine on cerebral ischemia-reperfusion injury.

Eligibility criteria: (1) Population (P): the target disease was not ischemic stroke, or the animal species were not rats or mice. (2) Intervention (I): the drugs used in the study were not ligustrazine, including mixed solution, combination with other drugs, etc. (3) Comparison (C): the control group was a non-blank control. Or another drug of unknown efficacy was used. (4) Outcome (O): the article did not report the relevant outcome indicators or the relevant data could not be obtained. (5) Study design (S): the types of articles are methodological research and non-original research, including review articles, reviews, conference reports, etc.

Information sources: The Cochrane Library, Embase, PubMed, and Web of Science were systematically searched.Results for all indicators in more than 2 studies were extracted. If multiple doses and courses were reported in an article, the maximum dose and longest course were extracted. If there is no data for relevant indicators in the article, we contact the author to obtain the original data. If the author refuses to provide the original data or does not respond, the public ruler software (https://apps.automeris.io/wpd/index.zh_CN.html) will be used to extract the data from the

relevant images. The mean, standard deviation or standard error of the relevant indicators were extracted.

Main outcome(s): Quantitative analysis showed that ligustrazine could effectively reduce the cerebral infarction volume, improve the neurological function after injury, and reduce the permeability of the blood-brain barrier. At the same time, the optimal dose and time of ligustrazine in the treatment of ischemia-reperfusion injury were determined by three-dimensional map. Qualitative analysis showed that ligustrazine ameliorated the injury induced by I/R mainly through anti-inflammatory response, oxidative stress and inhibition of cell apoptosis.

Quality assessment / Risk of bias analysis: The quality of the included articles was assessed by the CAMARADES 10-point scale.At the same time, the relevant items of the scale were modified to fit the characteristics of this research (D: allocation hiding [blinded induction of ischemia]; F: avoid the use of anesthetics with significant intrinsic neurotoxicity; G: animal model [ischemia and reperfusion]). Egger's rank correlation analysis was used to assess the publication bias of results. If | t| greater than 0.05, it shows that there is no significant publication bias, if |t|< 0.05, the trim and fill method was applied to determine the presence of publication bias.

Strategy of data synthesis: For the outcomes, the standardized mean difference (SMD) and 95% confidence interval (95%CI) were used to pool the results. When the value of SMD was greater than 0, it indicated that ligustrazine could improve this index, and when 95%CI was also greater than 0, it demonstrated that the improvement effect of ligustrazine on this index was statistically significant.
Heterogeneity was determined by Chi-square test, and I2 was used to quantify heterogeneity. When I250%, high heterogeneity was considered. The random effects model was used to combine the data, and subgroup analysis was used to explore the related sources of heterogeneity, including species. In

addition, sensitivity analyses were performed to determine whether the results were robust.

Subgroup analysis: Subgroup analyses according to rondent species are expected.

Sensitivity analysis: Sensitivity was used to evaluate the primary outcome.

Country(ies) involved: China.

Keywords: Ligustrazine; Ischemia-reperfusion injury; Preclinical evidence; Meta-analysis.

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