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Effectiveness and safety of glibenclamide for stroke: protocol for a systematic review and meta-analysis

Lihong Wen ,[1] Bin Huang,[2] Rong Tu,[1] Kunzhen Wan,[1] Hong Zhang,[1] Xiaoyun Zhang[1]

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LW and BH contributed equally.

LW and BH are joint first authors.

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[1]Emergency Department, Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Chengdu, China
[2]General Practice Department, Chengdu University of Traditional Chinese Medicine Affiliated Hospital, Chengdu, Sichuan, China

Correspondence to
Xiaoyun Zhang;
zhangxy1980@126.com and Hong Zhang;
30380997@qq.com

ABSTRACT

Introduction Despite the continuous improvement in modern medical treatment, stroke is still a leading cause of death and disability worldwide. How to effectively improve the survival rate and reduce disability in patients who had a stroke has become the focus of many investigations. Recent findings concerning the benefits of glibenclamide as a neuroprotective drug have initiated a new area for prospective studies on the effects of sulfonylureas. Given the high mortality and disability associated with stroke, it is essential to weigh the benefits of neuroprotective drugs against their safety. Therefore, the objective of the current study is to conduct a systematic review using meta-analysis to assess the benefits and safety of glibenclamide as a neuroprotective drug.

Methods and analysis This study will analyse randomised clinical trials (RCTs) and observational studies published up to 31 December 2020 and include direct or indirect evidence. Studies will be retrieved by searching PubMed, EMBASE, Web of Science, the Cochrane Library and China National Knowledge Infrastructure (CNKI) and WanFang Databases. The outcomes of this study will be mortality, scores from the Modified Rankin Scale and the occurrence of hypoglycaemic events. The risk of bias will be assessed using the Cochrane risk of bias assessment instrument for RCTs. A random-effect/fixed-effect model will be used to summarise the estimates of the mean difference/risk ratio using a 95% CI.

Ethics and dissemination This meta-analysis is a secondary research project, which is based on previously published data. Therefore, ethical approval and informed consent were not required for this meta-analysis. The results of this study will be submitted to a peer-reviewed journal for publication.

PROSPERO registration number CRD42020144674.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to analyse the benefits and safety of glibenclamide in patients who had a stroke based on data from both randomised clinical trials and observational studies.
- As is common with most meta-analyses, significant and unexplained heterogeneity may exist.
- The risk for ecological fallacy exists in this study as for any aggregate data meta-analysis.

INTRODUCTION

Rationale

Stroke is a common disease with high mortality and morbidity worldwide and often leaves survivors with severe neurological impairments and long-term disability.[1 2] According to data from The Third Cause of Death Survey in China, stroke is the leading cause of mortality and disability in adults in China. The stroke burden in China currently exhibits an explosive growth trend, which is characterised by rapid increases in stroke in low-income and younger individuals.[3] At present, the average incidence for the first stroke for residents in China aged 40–74 years has increased by an annual rate of 8.3%. The prevalence of stroke in adults in China aged 40 years or older has increased from 1.89% in 2012 to 2.19% in 2016, and it is estimated that 1.96 million people die due to the consequences of stroke every year.[4] Better prevention and treatment of stroke still face enormous challenges, and the medical system needs further improvement and optimisation. Therapies targeting the underlying pathophysiology of central nervous system (CNS) ischaemia and haemorrhage are conspicuously lacking. Several neuroprotective agents have been studied, but their clinical efficacy has been unsatisfactory.

Recent findings concerning the benefits of glibenclamide (GBC) as a neuroprotective drug have initiated a number of new prospective studies.[5] GBC is a member of the sulfonylurea class of drugs and has been used in the clinic as an oral hypoglycaemic agent.[6]

It exerts its pleiotropic protective effects on acute CNS injury by inhibiting the recently characterised Sur1–Trpm4 channel (formerly, the Sur1-regulated non-selective cation (NCCa–ATP) channel). GBC improves functional neurological outcomes in stroke models by protecting the microvascular

endothelium, reducing oedema formation and secondary haemorrhage, inhibiting neuronal cell death, maintaining the integrity of the blood–brain barrier (BBB) and promoting neurogenesis by blocking the Sur1–Trpm4 channel.[7 8] Thus, GBC has received renewed attention as a CNS treatment for ischaemic and haemorrhagic stroke and subarachnoid haemorrhage.[9–13] When studied in models of ischaemic stroke, GBC significantly reduced the mortality rate to 5%, whereas the vehicle-treated group exhibited 67% mortality at 24 hours. Compared with a decompressive craniectomy group, GBC significantly improved neurological function.[14–16]

GBC scavenges free radicals, reduces activated caspase-3 expression, increases the Bcl-2/Bax ratio and inhibits apoptosis by blocking NCCA channels to improve functional neurological outcomes in a rat model of intracranial haemorrhage (ICH).[17 18]Also, GBC can significantly reduce BBB permeability and markers of cell injury or cell death, protect the normal junctional localisation of Zonula Occludens 1 (ZO-1) and reduce inflammation and markers of inflammation, vasogenic oedema, and caspase-3 activation to improve functional neurological outcomes after subarachnoid haemorrhage.[18]

Several retrospective studies suggest that taking a sulfonylurea drug and continuing it following an ischaemic CNS insult significantly improve outcomes, including survival, greater functional independence, lower National Institute of Health Stroke Scale/Score (NIHSS) and less haemorrhagic transformation.[14 19] Administration of a sulfonylurea drug also improved long-term cognitive function in clinically relevant models of subarachnoid haemorrhage.[18] A prospective study suggested that intravenous GBC reduced water accumulation and mass effects after large hemispheric infarctions.[20] Another prospective study suggested that oral GBC is safe in treating acute hemispheric infarctions and potentially could prevent brain oedema and subsequent severe disability and death. Two studies[8 21] have suggested that GBC reduced oedema, protected BBB integrity and improved long-term neurological deficits. Another study reported that GBC reduced oxidative stress, inhibited apoptosis and improved neurological deficits.[22] However, a recent study tested a widely used GBC dose shown to be effective in other studies (10 µg/kg loading dose followed by 200 ng/hour for up to 7 days), and the result suggested that recovery from neurological impairments was not improved by GBC and also did not improve ICH outcomes.[23] Ghasami *et al* compared the use of GBC and insulin when given to patients with diabetes who had a haemorrhagic stroke and reported that GBC had no benefit compared with the insulin group.[24] However, we note that this was a small, non-randomised, non-placebo-controlled trial. Thus, further clinical work in haemorrhage is needed.

Objective

The primary objective of this study is to conduct a systematic review and meta-analysis of randomised clinical trials (RCTs) and observational studies to assess the safety and efficacy of GBC as a component of the medical treatment for patients who had a stroke and develop supporting evidence for effective clinical strategies.

METHODS

Study registration

This protocol is being conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25] or meta-analyses of healthcare interventions. The protocol report for this study follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) .[26] The PRISMA-P checklist is presented in online supplemental appendix 1.

Patient and public involvement statement

No patient involved.

Eligibility criteria

Studies meeting the following criteria will be included in the analysis: (1) RCTs and observational studies; (2) patients diagnosed with stroke using CT and MRI, including ischaemic and haemorrhagic stroke and subarachnoid haemorrhage; (3) an intervention group that will be treated with intravenous or oral GBC; (4) a comparison control group that will be included in the randomised trials, which will consist of a placebo, blank or others; (5) data concerning mortality and other major adverse events; and (6) studies published up to 31 December 2020.

Direct comparisons will be made from the identified studies that include a placebo or other control compounds. RCTs and observational studies will be screened for eligibility. Whether both types of studies should be included to conduct the meta-analysis is dependent on the circumstances because it has been suggested recently that RCTs and observational studies should not be analysed in isolation.[27] Therefore, the inclusion of selected RCTs and observational studies in the meta-analysis is dependent on the quality assessment.

Information sources

The following databases will be searched from their inception forward for potentially eligible studies without language restrictions and published up to 31 December 2020: (1) PubMed, (2) Scopus, (3) Web of Science, (4) Cochrane Central Register of Controlled Clinical Trials, and (5) CNKI and WanFang Databases. We also will manually search references from relevant randomised clinical trials identified through systematic reviews, meta-analyses and studies included in this review.

Search strategy

A systematic search of six public domain databases mentioned above will be performed. The first author will conduct all database searches without language restrictions. The search strategies will be adapted from previous research and developed using text words and medical

subject headings. We will use exploded medical subject headings and appropriate corresponding keywords related to the population, combined with exposure and outcomes, such as 'Stroke' OR 'intracerebral hemorrhage' OR 'ischemic Stroke' OR 'cerebral infarction' OR 'Hemorrhagic stroke' OR 'subarachnoid hemorrhage' AND 'Glibenclamide' AND 'prognostic' OR 'modified Rankin Scale'. A sample search strategy for PubMed is shown in online supplemental appendix 2.

Study records

Study selection

All studies will be extracted from electronic databases using the search strategy described above and imported into EndNote V.X7 software (Thomson Reuters, Canada). Duplicate studies will be removed. Two authors will select studies independent of each other. Complete articles will be retrieved for all titles and abstracts that appear to meet the inclusion criteria or where any uncertainty exists. The two reviewers (LW and BH) will list all the studies to be included and document the primary reasons for excluding studies that do not conform to the inclusion criteria. Disagreements between the two authors will be resolved by discussing with the third author (RT) and, if necessary, consulting with the fourth author (KW). The overall agreement rate prior to correcting for discrepancies will be calculated using Cohen's kappa (κ) statistics. A flow diagram will be constructed that depicts the search process. An online supplemental file containing a reference list of all excluded studies, including the reason(s) for exclusion, will be included in the study. We will show the details of the selection process in the PRISMA flow chart. The proposed structure for the flow diagram is shown in figure 1.[26]

Data acquisition

Before initiating data acquisition, a codebook will be developed in Microsoft Excel 2013. Two independent researchers will extract data. The following data will be extracted from each eligible study using a standardised data collection form: (1) study characteristics, including publication year, author, country of the study, type of study (RCT, cohort, case–control and others), sample size, follow-up duration and others; (2) participant characteristics, including age, sex, stroke type (ischaemic or haemorrhagic stroke or subarachnoid haemorrhage) and baseline condition of participants (eg, disease severity: NIHSS will be used to gauge disease severity); (3) intervention characteristics, including name of the drug(s), dose, route of administration and others; (4) control characteristics, including the type of drug(s) used, dose, route of administration and others; and (5) outcome data for mortality, Modified Rankin Scale (mRS) and occurrence of hypoglycaemic events. The first two authors will acquire the data from the selected studies, independent of each other, using the codebook in Microsoft Excel. After data acquisition, both authors will review the codebooks and resolve discrepancies by consensus. If a consensus cannot be reached, the third author will

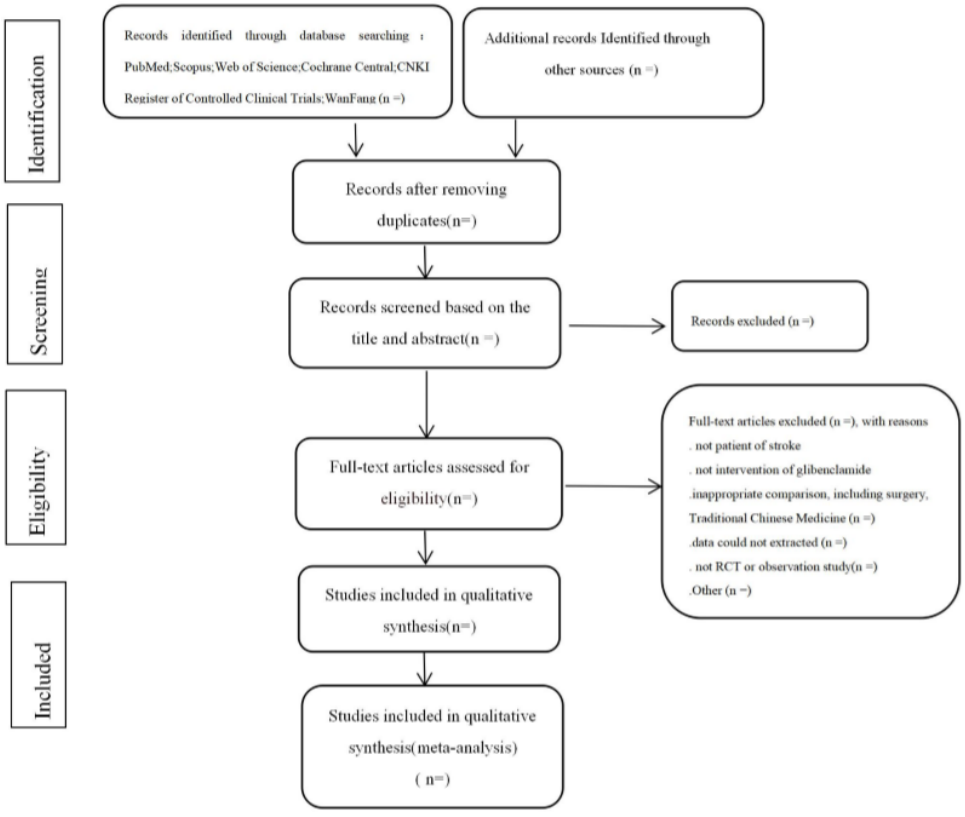

Figure 1 Flow diagram of study selection process.

Table 1 Covariates that will be included in the study.

Studies characteristics	Publication year, author, country of the study, type of study (randomised clinical trial, cohort, case–control and others), sample size, follow-up duration and others
Participant characteristics	Age, sex, stroke type (ischaemic or haemorrhagic stroke or subarachnoid haemorrhage) and baseline condition of participants (eg, underlying disease and medication history)
Intervention characteristics	Name of the drug, dose, and route of administration (oral or intravenous)
Control characteristics	Type of the drug, dose, and route of administration
Outcome	Mortality, Modified Rankin Scale and occurrence of hypoglycaemic events

provide a recommendation. A complete list of covariates that we will include is shown in table 1.

OUTCOMES

The outcomes will include mortality, mRS and the occurrence of hypoglycaemic events.

Assessment of the quality of the evidence

According to the Grading of Recommendations Assessment, Development and Evaluation, the quality of included studies will be assessed using the online guideline development tool (http://gdt.guideline-development.org/) and divided into four levels of quality: high, moderate, low and very low.[28]

Risk of bias assessment in individual studies

Risk of bias for RCTs will be assessed using the Cochrane risk of bias instrument[29], which contains seven specific domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other biases. This instrument assesses the methodological quality of the RCTs concerning low risk, high risk or unclear risk of bias.[29] If any domain is scored high/low risk of bias, the study will be considered high/low risk of bias. No study will be excluded based on the results of the risk of bias assessment.[30] The first two authors will conduct all risk of bias assessments independent of each other. Then, the two authors will review the results for the risk of bias assessment and resolve any discrepancies by consensus. If a consensus cannot be reached, the third author will be consulted.

The nine-item Newcastle–Ottawa Quality Scale is widely used to assess the quality of non-randomised trials using risk evaluation for the adequacy of selection, comparability, and outcomes assessment.[31] The high-quality studies will be defined as studies with a score that is greater than or equal to six.

Data synthesis and analysis

Data synthesis

Review Manager V.5.3 (Cochrane Collaboration) and Stata V.16.0 software will be used to conduct this meta-analysis. The mean difference or standardised mean difference with 95% CIs is used to calculate continuous variables.

Assessment of heterogeneity

Statistical heterogeneity among included studies will be assessed using the χ^2 test and I^2 test. Initially, we will use a fixed-effect model for data analysis. If $I^2 > 0.5$ or $p<0.1$, this will indicate the presence of significant heterogeneity among the studies, and a random-effect model will be used without examining the probable cause for the high heterogeneity.

Subgroup analysis

If there is considerable heterogeneity and the data are sufficient, subgroup analyses will be conducted to identify potential causes for the heterogeneity. Subgroup analyses will be performed based on the type of stroke (ischaemic stroke, haemorrhagic stroke, or subarachnoid haemorrhage) and time to treatment.

Assessment of publication bias

Publication bias will be examined according to the funnel plot method. Also, Egger's test and Begg's test will be conducted to assess the publication bias quantitatively using Stata V.16.0 software.

Sensitivity analysis

We will conduct sensitivity analyses of the primary results to explore the robustness of the review conclusions, if feasible, after considering the impact of methodological quality, missing data and sample size. According to the Cochrane Handbook, when a sufficient number of original studies are included (generally more than ten trials), publication bias analysis will be performed using a funnel plot. A symmetrical funnel plot indicates low publication bias. If the funnel plot is asymmetrical, that will indicate a high risk for publication bias.

Software used for data analysis

All data will be analysed using Stata/IC for Mac V.16.0.

REGISTRATION

In accordance with the PRISMA-P, our systematic review with network meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 28 April 2020.

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Contributors LW and BH drafted the manuscript. RT and KW contributed to the development of the data sources to search for relevant literature, including the search strategy, selection criteria, data extraction criteria and risk of bias assessment strategy. HZ provided statistical expertise, and XZ, BH and HZ provided content expertise on glibenclamide and stroke. All four authors read, provided feedback and approved the final manuscript.

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ORCID iD

Lihong Wen http://orcid.org/0000-0001-9445-4932

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