

# BMJ Open Efficacy and safety of edaravone for acute intracerebral haemorrhage: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Intracerebral haemorrhage (ICH) is a life-threatening condition with no effective internal treatment options. However, edaravone is a promising therapeutic agent, although its beneficial effects are inconclusive based on previous systematic reviews and meta-analyses. While several trials in the last 8 years have reported the favourable long-term functional outcomes, a few reports indicated edaravone to be associated with an increase in adverse events.

**Methods and analysis** This protocol was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We will perform the comprehensive and manual search for published articles, ongoing trials, dissertations and grey literature. The following databases will be searched from inception to 23 April 2020: Medline, Embase, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Chinese scientific periodical database of VIP INFORMATION, Wanfang Data and SinoMed, with no language restrictions. All randomised controlled trials that (1) compared edaravone with placebo or no treatment, and (2) compared edaravone plus routine treatment or cointervention with routine treatment or cointervention for treating acute ICH will be included. Mortality and long-term dependency will be the primary outcomes. The incidence of adverse events will be assessed for safety evaluation. Two reviewers in pairs will independently carry out the article selection, data extraction and quality assessment. Assessment of the risk of bias and data synthesis will be performed using software Review Manager V.5.3. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the quality of the overall evidence.

**Ethics and dissemination** There are no ethical considerations associated with this updated systematic review and meta-analysis. The findings will be disseminated in peer-reviewed journals or conference presentations.

**PROSPERO registration number** CRD42019147801.

## INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) is the second most common type of

## Strengths and limitations of this study

- A well-recognised approach for conducting and reporting systematic reviews and meta-analysis will be followed (Cochrane handbook).
- New trials published in the recent 8 years will be added in this updated systematic review and meta-analysis and the efficacy and safety of edaravone for treating intracerebral haemorrhage will be comprehensively assessed.
- Long-term functional status and mortality will be mainly focused on as the primary outcomes in this review for the evaluation of edaravone.
- Due to the evaluation of various timepoints, dose and duration of edaravone treatments, the findings are likely to be heterogeneous.
- Since different scales were used for outcome assessment, a pooled analysis of all included studies could be challenging.

stroke, affecting 18.8%–47.6% of individuals across different races.<sup>1–3</sup> It is usually caused by the rupture of small penetrating arteries leading to cerebral parenchymal bleeding which can extend into the ventricular, even subarachnoid space.<sup>4 5</sup> Though there have been significant advances in the detection and management of ICH, the clinical outcomes are still not encouraging.<sup>5 6</sup> Given that ICH is life threatening and can lead to higher mortality and more severe disability compared with ischaemic stroke, it is considered to be the most dangerous subtype of stroke.<sup>7</sup> Nearly 40% and 54% of the patients will die within the first month and the first year, respectively, after the onset of ICH.<sup>8</sup> Though survived, patients would suffer from various degrees of disability and other neurological complications additionally. Although important advances have been made in the areas of basic and clinical research, there are still no recommended effective internal medical treatments for ICH. Neuroprotection

of the surrounding brain tissue from the degenerative effects of the haematoma is a suggested approach,<sup>9</sup> which is yet to be validated.

Pathological mechanisms underlying ICH are commonly categorised into (1) primary injury which refers to a direct injury caused by mass effect of the haematoma or by neurovascular disruption, and (2) secondary injury that involves in the cascade events triggered by the primary injury and its metabolites.<sup>7</sup> The coagulation cascade (especially thrombin), haemoglobin breakdown products, inflammation and free radicals all contributed to ICH-induced injury.<sup>10</sup> Free radical-induced damage is considered to be particularly deleterious, and clinical trials have assessed the potential of free radical scavengers to ameliorate the damage.<sup>11</sup>

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger<sup>12–16</sup> that was initially approved for treating acute ischaemic stroke (AIS) in Japan.<sup>17 18</sup> Based on the similar pathological process of AIS and ICH, edaravone was tested in ICH models. It was shown to improve the neurological deficits in ICH models via anti-inflammatory and antiapoptotic mechanisms, attenuating the ICH-induced brain oedema and oxidative injury, as well as reducing iron-induced and thrombin-induced brain injury.<sup>19–21</sup> Additionally, edaravone is reported to demonstrate obvious neuroprotective effects in patients with ICH and has been widely used in clinic.<sup>17 22 23</sup>

Considering the differences in the pathology of ICH and AIS, it is important to evaluate the specifics of edaravone therapy for ICH, which include the right time to start treatment, optimal dose and duration of treatment. Basic studies have shown that compared with AIS, treatment of ICH requires higher doses of edaravone, indicating its dose-dependent neuroprotective effects.<sup>19 20 24 25</sup> However, the dose of edaravone for ICH treatment in previous systematic review and meta-analysis was similar to that for AIS.<sup>26</sup> Moreover, these previous studies only showed edaravone alleviating neurological function deficits,<sup>26 27</sup> while its effect on survival or dependency at the end of long-term follow-up was not reported. Over the past 8 years, emerging evidence from several randomised controlled trials (RCTs) suggested that edaravone may be effective in treating ICH by improving the activities of daily living, as well as by not increasing mortality and incidence of adverse effects.<sup>28–30</sup> The common adverse effects associated with the use of edaravone include mild impairment of kidney and liver function, skin irritation and arrhythmia.<sup>31 32</sup> Furthermore, edaravone is a relatively expensive drug, costing approximately US\$600–860 for one standard course of treatment per stroke patient in China.<sup>26</sup> It is worth noting that despite more than 200 trials have been reported in the last 8 years, the current status of edaravone as a therapeutic agent for ICH remains controversial, which warrants a systematic review and meta-analysis. Under these urgent circumstances, we decided to perform this updated systematic review and meta-analysis to obtain conclusive evidence in support of edaravone for ICH treatment.

## Objectives

This updated systematic review and meta-analysis aims at systematically analysing all of the RCTs to evaluate the efficacy and safety of edaravone for patients with acute ICH. Moreover, it aims to provide the best available evidence to enable both physicians and patients to make an informed choice regarding treatment for ICH.

## METHODS AND ANALYSIS

This protocol describes the procedure for a systematic review and meta-analysis of RCTs that reported the use of edaravone for the treatment of ICH. This protocol was performed following the reporting items listed in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols,<sup>33 34</sup> which was established to facilitate the preparation and reporting of a robust protocol for a systematic review and meta-analysis. The anticipated start date of this study is 23 April 2020.

### Eligibility criteria

- Types of studies
 

RCTs with or without blinding will be included in this study. Non-RCTs, studies with the cross-over design, and uncontrolled clinical trials will be excluded.
- Types of participants
 

Adult patients with acute ICH (within seven days) confirmed by CT or MRI according to a guideline for healthcare professionals from the American Heart Association/American Stroke Association<sup>9</sup> will be included. There will be no restrictions in terms of the patients' age, gender, race, education or economic status. Patients with traumatic haemorrhagic stroke, primary intraventricular haemorrhage and subarachnoid haemorrhage will be excluded.
- Types of intervention
 

We will mainly focus on the intervention that edaravone was compared with the placebo or no treatment. Additionally, trials wherein routine treatments or cointerventions with edaravone were administered equally to all groups will also be included. However, there will be no restriction on the course of treatment.
- Types of outcome measures
 

As ICH is a life-threatening condition with a high rate of disability, we will pay more attention to mortality and the long-term functional status in this systematic review. Clinical studies that reported numerical data on one or more of the following outcomes will be considered.

  - Primary outcomes
 

All-cause mortality and dependency at the end of the follow-up will be set as the primary outcomes. The functional status was assessed using clinical scales including the modified Rankin Scale (mRS), Glasgow Outcome Scale (GOS) and Barthel Index (BI). The dependency will be defined as mRS grades 3–6, GOS grades 1–3, or BI less than or equal to 60.
  - Secondary outcomes

The secondary outcomes will include: (1) improvement of neurological impairment assessed using clinical scales including the National Institute of Health Stroke Scale, Canadian Neurological Scale, European Stroke Scale, Scandinavian Stroke Scale, Modified Edinburgh-Scandinavian Stroke Scale and other related scales, (2) the total efficiency rate including cure rate, obvious effective rate and effective rate, and (3) reduction in the haematoma volume.

### 3. Safety outcome

Adverse effects of edaravone including impairment of kidney and liver function, skin irritation, nausea, will be evaluated.

### Search strategy

We will conduct the comprehensive electronic searches of Medline, Embase and Cochrane Central Register of Controlled Trials. Given that edaravone is widely used in China, we will search the following Chinese databases: China National Knowledge Infrastructure, Chinese scientific periodical database of VIP INFORMATION, Wanfang Data and SinoMed from their respective inception dates to 23 April 2020. In addition, we will also search for clinical trial registers, dissertations and grey literature.<sup>35</sup> We will develop the search strategy for Medline (see online supplementary appendix 1. Search Strategy Example) and the equivalent search words will be used in other databases as well. The registers which mainly include ongoing or unpublished trials are the following:

- ▶ WHO International Clinical Trials Registry Platform.
- ▶ ClinicalTrials.gov.
- ▶ The United Kingdoms' ISRCTN registry (ISRCTN).
- ▶ Chinese Clinical Trial Registry.
- ▶ Australia and New Zealand Clinical Trials Registry.
- ▶ The Netherlands Trial Register.
- ▶ German Clinical Trials Register.
- ▶ Japan Primary Registries Network.
- ▶ Clinical Trials Registry—India.
- ▶ Iranian Registry of Clinical Trials.
- ▶ Sri Lanka Clinical Trials Registry.

Our research will be restricted to humans and clinical trials, with no language restrictions.

### Screening and selection

Duplicate articles will be removed after identifying them by database searching. Two review authors (LF, TL) will independently screen the articles for titles and abstracts according to the inclusion criteria. The full text will be reviewed if necessary. In addition to this, the list of related studies from the references will be examined further to identify other potential studies to be included. The reviewers will exclude reports that are irrelevant to our research and retrieve full-text articles for the remaining references. The same two reviewers will independently screen these full-text articles to identify studies for inclusion, as well as determine and record reasons for the exclusion of ineligible studies. They will resolve any disagreements through discussion or, if required, they

will consult a third review author (YG) to arbitrate when disagreements are not resolved. The excluded studies will be listed in a table with the proper reasons. The whole process of study screening and selection is shown in figure 1.

### Data extraction

Two review authors (QY, PJ) will independently extract data on methods, patients, interventions, outcomes and results from the included studies, using a preformulated data collection form. We will try to contact the corresponding authors for any missing data or clarification on unclear information.<sup>35</sup>

### Quality assessment

The methodological quality assessment of the eligible studies will be independently conducted by two reviewers (LF, NL) for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>35</sup> Disagreements will be resolved by discussion or by involving another review author (YG). The risk of bias will be assessed according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. The risk of bias for each domain will be classified into three levels: low risk, high risk and unclear. Unclear items in studies will be inquired by contacting the corresponding authors for details. We will provide information from the study report together with a justification for our judgement, in the 'risk of bias' tables.

### Data synthesis and management

#### 1. Measures of treatment effect

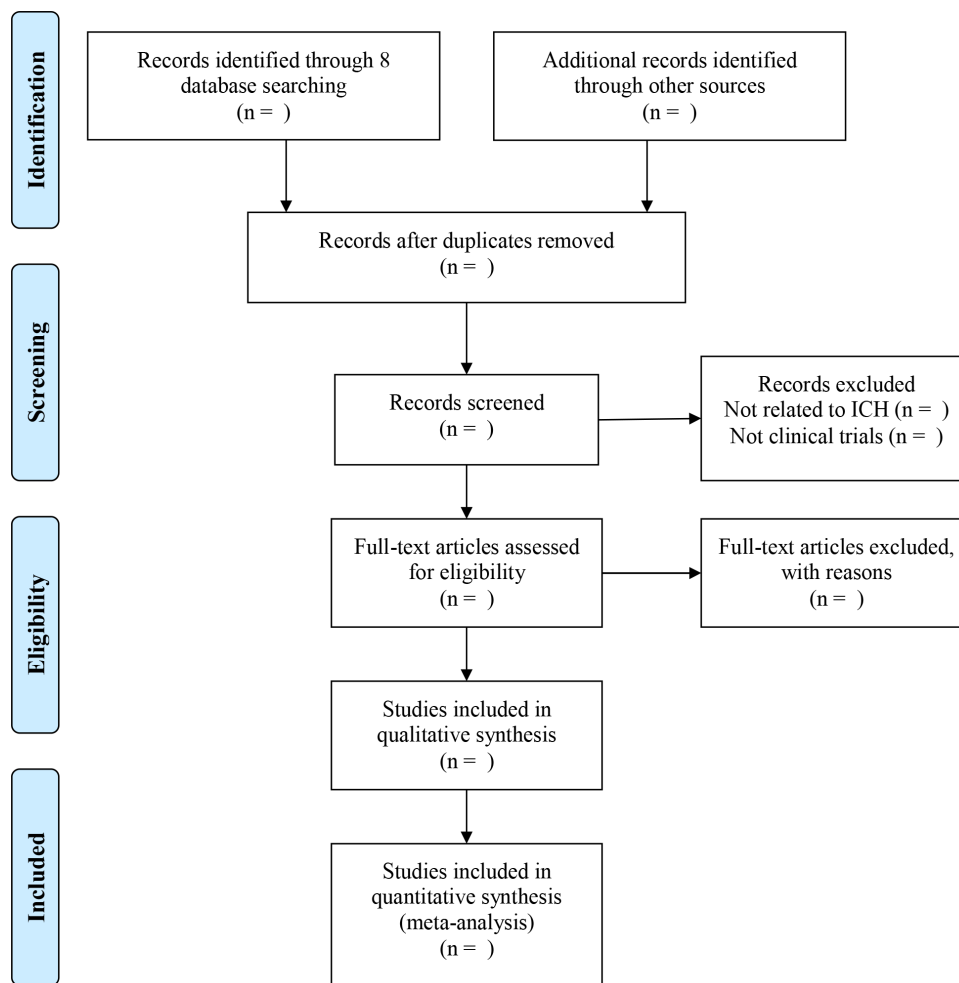
We plan to summarise the data using risk ratio calculations and 95% CIs for dichotomous outcomes and mean differences with 95% CIs for continuous outcomes in the final analysis. We will calculate standardised mean differences with 95% CIs when different scales were used to measure the same continuous outcome variable.

#### 2. Dealing with missing data

The corresponding author will be contacted by reviewers via email or telephone to obtain the missing data or information which was not clearly described. In case the missing data are unavailable, intention-to-treat and sensitivity analyses will be performed to address the potential impact of the missing data,<sup>36 37</sup> which will then be discussed if necessary.

#### 3. Assessment of heterogeneity and data synthesis

Statistical heterogeneity among the included trials will be evaluated using the  $I^2$  test. A meta-analysis will be conducted if there is no significant clinical (relating to the participants, interventions, controls and outcomes) and statistical heterogeneity ( $I^2$  values are less than 75%) between the included trials. However, if the  $I^2$  value is less than 25%, we will use a fixed-effect model to synthesise the data, and if it is between 25% and



**Figure 1** Flow diagram of the study selection process. ICH, intracerebral haemorrhage.

75%, we will estimate the sources of the heterogeneity. If the statistical heterogeneity is explained successfully by sensitive analysis or subgroup analysis (ie,  $I^2$  is less than 25%), we will also use the fixed-effect model to synthesise the data. Otherwise, a random-effect model will be applied. Data will not be synthesised if there is a significant level of statistical heterogeneity among the trials (ie,  $I^2$  is greater than 75%) that cannot be explained or handled by subgroup analysis. All statistical analyses will be performed using Review Manager V.5.3 (The Cochrane Collaboration) software.

#### 4. Analysis of subgroups or subsets

If the data are available for the subgroup analyses, we will plan to compare:

- Effects in patients with various dose of edaravone (less than 60 mg/day, 60 mg/day and more than 60 mg/day);
- Effects in patients with various course of treatment (less than 14 days, 14 days and more than 14 days);
- Effects in patients with various drug combinations (edaravone plus nimodipine, and edaravone plus other neuroprotective agents);
- Effects in patients with various types of ICH based on Structural lesion, Medication, Amyloid angiopathy,

Systemic/other disease, Hypertension, Undetermined aetiological classification;

- Effects in patients with various course of disease (within 24 hours and after 24 hours from stroke onset);
- Effects in patients with various haemorrhage sites (brain stem, cerebellum, basal ganglia region and other sites).

#### 5. Assessment of reporting biases

A funnel plot will be generated to explore the possibility of publication bias if 10 or more trials are included per comparison.

#### Confidence in cumulative evidence

The strength of the body of evidence in this review will be categorised as high, moderate, low or very low according to the Grading of Recommendations Assessment, Development and Evaluation system<sup>38</sup> using the GRADEpro software.

#### Patient and public involvement

Not applicable. This protocol of systematic review and meta-analysis does not directly involve patients and the general public. Data will be collected from published articles retrieved from main databases and manual search.

## ETHICS AND DISSEMINATION

There are no ethical considerations associated with this updated systematic review and meta-analysis. The findings will be disseminated in peer-reviewed journals or conference presentations.

## DISCUSSION

The long-term clinical outcomes of edaravone therapy remain unclear despite its benefits in the basic management of ICH. Neuroprotective agents developed based on the specific pathological mechanism are potentially beneficial for ICH treatment.<sup>9</sup> Edaravone is widely used in China, and is even mentioned in the Chinese guidelines for acute ICH management.<sup>39</sup> Previous meta-analyses have shown edaravone to be effective only in improving neurological impairment for patients with ICH.<sup>26 27</sup>

Free radical injury is involved in the pathological process of both ICH and AIS, though it may be induced at different timepoints in the two conditions. Edaravone acting as a free radical scavenger is effective for AIS when administered during a specific time window. Therefore, the optimal time for initiating the edaravone treatment, the proper dose and duration of treatment for ICH deserve to be studied in depth. Besides, improvement of neurological deficits is the surrogate outcome when it comes to the assessment of specific treatment for stroke, and lacks robust support strength. Mortality and functional status after the long-term follow-up measured with mRS, GOS and BI should be the most important outcomes when evaluating the treatment efficacy of new therapeutic agents. However, previous meta-analyses do not address these issues due to the lack of reports in the previously included articles.<sup>26 27</sup> After adding new clinical reports to this updated systematic review and meta-analysis, we will mainly focus on long-term functional status and mortality as primary outcomes for the evaluation of edaravone.

This protocol has some potential limitations. Various timepoints, dose and duration of edaravone usage in clinical trials may lead to heterogeneous findings. As different scales were used for outcome assessment, it may be impossible to perform a pooled analysis of all included studies. Subgroup analyses, however, will be performed according to the different therapeutic schedules and different outcomes measurements if data are available. Additionally, we will interpret the results with caution and take a critical approach when assessing the overall evidence.

In conclusion, the systematic review and meta-analysis we proposed will help update the existing evidence on the benefits and harms of edaravone treatment for ICH, thereby enabling patients, research fellows and clinical physicians to make the proper choice regarding treatment for ICH.

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**Contributors** YG put forward the conception of the study. LF and NL designed the study. LF drafted the protocol and then it was revised by NL, SG, CZ and YG.

LF and TL will independently screen the potential studies, and then LF and NL will independently assess the risk of bias of the included studies. YG will arbitrate any disagreements during the review. QY and PJ will extract data. LF will perform data synthesis. All authors have read and approved the final submitted version of this protocol.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

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