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Efficacy and Safety of Edaravone for Acute Intracerebral Hemorrhage: Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Intracerebral hemorrhage (ICH) is a life-threatening disease with unoptimistic treatment conditions. Edaravone might be a promising medical therapy without sufficient evidence. Previous systematic reviews and meta-analyses indicated the beneficial or deleterious effect of edaravone is inconclusive. Lots of trials have been published in recent 8 years and several of them reported the favorable long-term function outcome whereas a few reports indicated the increase in the rate of adverse events, warranting an update of a systematic review.

Methods and analysis: This protocol was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We will conduct the comprehensive electronic search and manual search for

published articles, ongoing trials, dissertations, and gray literature. All randomized controlled trials in which edaravone was compared with placebo, no treatment, other medicine, or edaravone plus routine treatment, edaravone plus co-intervention was compared with routine treatment or co-intervention alone for treating acute ICH will be included without language restriction. Mortality and long-term disability will be set as the primary outcome. 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 risk of bias and data synthesis will be performed using software Review Manager 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.

ARTICLE SUMMARY

Strengths and limitations of this study

1) Well-recognized approach for conducting and reporting systematic reviews and meta-analysis will be followed (Cochrane handbook).
2) New trials published in recent 8 years will be added in this updated systematic review and meta-analysis and the efficacy and safety of edaravone for treating intracerebral hemorrhage will be comprehensively assessed.
3) Long-term functional status and mortality will be mainly focused on in this review.
4) The quality of selected articles will be one of the anticipated limitations.

Word count: 2592

INTRODUCTION

As the second common type of stroke, nontraumatic intracerebral hemorrhage (ICH) accounts for a proportion from18.8% to 47.6% in different races.[1-3] ICH is usually caused by rupture of small penetrating arteries and the followed cerebral parenchymal bleeding may also extend into ventricular, even subarachnoid space.[4 5] The recognition and management of ICH have been rapidly developed whereas the situation is still unoptimistic.[5 6] Given that ICH is so dangerous and life-threatening that it leads to higher mortality and more severe disability compared with ischemic stroke, it's considered to be the most dangerous subtype of stroke.[7] Nearly 40% and 54% of patients will die in the first month and in the first year after onset respectively.[8] Though survived, patients would suffer from various degrees of disability and other neurological complications additionally. It's closely helpless and it deserved to make vast progress in ICH treatment strategy. Although important advances have been made in basic and clinical research about ICH, unfortunately, there is no specific recommend effective internal medical treatment at present. It's noted that a rational but still unproven approach to acute ICH treatment is neuroprotection of surrounding brain tissue from the toxic effects of the hematoma.[9]

Pathological mechanisms of ICH are commonly divided into primary injury which refers to direct injury by mass effect of the hematoma or by neurovascular disruption, and secondary injury that involves in the cascade events triggered by primary injury and its metabolites.[7] The coagulation cascade (especially thrombin), hemoglobin breakdown products, inflammation and free radicals all participate in ICH-induced injury.[10] Free radicals induced damage is considered to be important in the pathological progress of ICH particularly, and efforts have been made to ameliorate the damage with free radical scavengers in clinical trial.[11]

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger aiming at scavenging free radicals.[12-16] It was initially permitted in treating acute ischemic stroke (AIS) in Japan.[17 18] Based on the similar pathological process of AIS and ICH, basic researches showed edaravone had scavenging properties that improved neurological deficits in ICH models via multiple effect, such as anti-inflammatory and anti-apoptosis mechanisms,

attenuating ICH-induced brain edema and oxidative injury, reducing iron- and thrombin-induced brain injury and so on.[19-21] Additionally, edaravone is reported to demonstrate obvious neuroprotective effects in ICH patients and it has been widely used in clninic.[17 22 23]

Considered that there are some differences between the pathophysiology of ICH and that of AIS, when for initiating edaravone is the exact time, what dosage is proper choice, and how long is the enough course of treatment are still unclear and these clinical issues attract more attention of physicians. Related basic researches showed usage of edaravone in ICH is higher than that in AIS which displayed the dosage-dependent neuroprotective effect of edaravone,[24 25 19 20] however, the dosage of edaravone for ICH treatment in previous systematic review and meta-analysis was similar to that of AIS because of the included articles didn't mention that.[26] Besides, it's reported that edaravone for treating ICH merely showed the potential benefit in alleviating neurological function deficits.[26 27] Death or dependency at the end of long-term follow-up which owns more robust support strength for evaluation of medicine efficacy was not reported and they needs further study. Over the past 8 years, emerging evidence of several randomized controlled trials (RCTs) suggested that edaravone may be effective for ICH treatment by improving the activity of daily living after the long-term follow-up as well as no increase in mortality and adverse effects.[28-30] However, related retrospective researches reported the use of edaravone in ICH treatment showed common adverse effects such as mild impairment of kidney function, mild impairment of liver function, skin irritation, and arrhythmia.[31 32] What's more, edaravone is a relatively expensive treatment in terms of medical costs, and it costs approximately 600 to 860 USD for one standard course of treatment per stroke patient in China.[26] It's worth noting that there are many confused issues unanswered, and the current condition that edaravone for ICH treatment is still controversial at present. More than 200 trials with potential evidence have been reported in recent 8 years, warranting a systematic review and meta-analysis update. Under the urgent circumstances, we are decided to perform this updated systematic review and meta-analysis to obtain the conclusive evidence of edaravone for ICH treatment.

OBJECTIVE

This updated systematic review and meta-analysis is aiming at systematically analyzing all the RCTs to evaluate the efficacy and safety of edaravone for patients with acute ICH, aiming at providing the best available evidence, so as to provide the proper choice for both physicians and patients.

METHODS

Our protocol of systematic review and meta-analysis was registered in the International Prospective Register of Systematic Review (PROSPERO), and the registration number was CRD42019147801 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019147801). This protocol was performed following the reporting items listed in the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P),[33 34] which was established aiming at facilitating the preparation and reporting of a robust protocol for the systematic review and meta-analysis. The anticipated start date of this study is 01/06/2020.

Eligibility criteria

1. Types of studies

RCTs with or without blinding, including cross-over designs and pragmatic trials, will be included in this study. Non-RCTs and uncontrolled clinical trials will be excluded.

2. Types of participants

Adult patients who suffered from acute ICH (within 7 days) as diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) will be included according to a guideline for healthcare professionals from the American Heart Association/American Stroke Association.[9] There are no restrictions on the patients in terms of age, gender, race, education or economic status. Patients with traumatic hemorrhagic stroke, primary intraventricular hemorrhage, and subarachnoid hemorrhage will be excluded.

3. Types of intervention

We will mainly focus on the intervention with edaravone which was compared with placebo, no treatment, the other medical treatment for acute ICH patients. Besides, routine treatment or co-interventions will also be allowed when the routine treatment or co-interventions are administered equally to all intervention groups of a trial. There is no restriction on the course of treatment.

4. Types of outcome measures

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

4.1 Primary outcome

All-cause mortality and improvement of functional status will be set as the primary outcome at the end of follow-up. The functional status was assessed with clinical scales including modified Rankin Scale(mRS), Glasgow Outcome Scale(GOS) and Barthel Index(BI). The favorable functional status will be defined as mRS grade less than 3, GOS grade more than 3 or BI score more than 60.

4.2 Secondary outcomes

The secondary outcomes include: 1) the improvement of neurological impairment assessed with clinical scales including National Institute of Health Stroke Scale (NIHSS), Canadian Neurological Scale (CNS), European Stroke Scale (ESS), Scandinavian Stroke Scale (SSS), Modified Edinburgh-Scandinavian Stroke Scale (MESSS) and other related scales; 2) The proportion of total efficiency rate including cure rate, obvious effective rate, and effective rate. 3) Reduction of hematoma volume.

4.3 Safety outcome

Adverse effects of the edaravone including impairment of kidney function, impairment of liver function, skin irritation, nausea, to name a few.

Search strategy

We will conduct the comprehensive electronic searches of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL). Given that edaravone is widely used in China, we will search the following Chinese databases: China National Knowledge Infrastructure (CNKI), Chinese scientific periodical database of VIP INFORMATION, Wanfang Data, China biomedical literature service system from their respective inception dates to present. In addition, we will search clinical trial registers, dissertations, and gray literature.[35] We will develop the search strategy for MEDLINE (see supplementary material online supplementary Appendix 1. Search Strategy Example) and the equivalent search words will be used in other databases.

The registers which mainly include ongoing or unpublished trials come as followed:

1) World Health Organization International Clinical Trials Registry Platform (ICTRP),
2) ClinicalTrials.gov,
3) The United Kingdoms' ISRCTN registry (ISRCTN),
4) Chinese Clinical Trial Registry (ChiCTR),
5) Australia and New Zealand Clinical Trials Registry (ANZCTR),
6) The Netherlands Trial Register (NTR),
7) German Clinical Trials Register (DRKS),
8) Japan Primary Registries Network (JPRN),
9) Clinical Trials Registry – India (CTRI),
10) Iranian Registry of Clinical Trials (IRCT),
11) Sri Lanka Clinical Trials Registry (SLCTR).

Our research will be restricted to studies conducted in humans and clinical trials, while there will be no language restriction.

Screening and selection

The duplicate articles will be removed after the records identified through database searching. Two review authors (LDF, TTL) will independently screen the articles in terms of titles and abstracts of articles according to the inclusion criteria. The full text will be reviewed if necessary. In addition to this, the obtained references list of related studies will be examined further for other potential studies to be included as a result of our searching activities. The reviewers will exclude reports that are obviously irrelevant to our research. They will retrieve full-text articles for the remaining references, and, independently, the same two review authors will screen these full-text articles to identify studies for inclusion, and identify 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 had not been resolved. The excluded studies will be listed in a table with proper reason. The whole study screening and selection is shown in Figure 1.

Data extraction

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

Quality assessment

The methodological quality assessment of the eligible studies will be independently conducted by two reviewers (LDF, NL) for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[35]. They will resolve any disagreements by discussion or by involving another review author (YG). 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 assessments about 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 corresponding authors for details with effort. We will provide information from the study report together with a justification for our judgment, in the 'Risk of bias' tables.

Data synthesis and management

1) Measures of treatment effect

We plan to summarize the data using risk ratio (RR) calculations and 95% confidence intervals (CIs) for dichotomous outcomes, and we intend to use mean differences (MDs) with 95% CI for continuous outcomes in the final analysis. We will calculate standardized mean differences (SMDs) 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 e-mails and telephone call to obtain the missing data or information which was not clearly described. The intention-to-treat analysis will be performed if possible, and a sensitivity analysis will be conducted to address the potential impact of missing data when the missing data are unobtained.[36 37] The impact of missing data will be discussed if necessary.

3) Assessment of heterogeneity and data synthesis

Statistical heterogeneity amongst the included trials will be evaluated using the I^2 test, and a meta-analysis will be conducted if there proves to be 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. If the I^2 value is, however, less than 25%, we will use a fixed-effect model to synthesize the data, and if it is between 25%-75%, we will estimate the sources of the heterogeneity. If the statistical heterogeneity is

explained successfully by sensitive analysis or subgroup analysis (i.e., I^2 is less than 25%), we will also use the fixed-effect model to synthesize the data, otherwise, a random-effects model will be applied. Data will not be synthesized if there is a significant level of statistical heterogeneity amongst the trials (i.e., I^2 is greater than 75%) which is not possible to explain or to handle (by subgroup analysis). All statistical analyses will be performed using Review Manager 5.3 (The Cochrane Collaboration) software.

4) Analysis of subgroups or subsets

We will conduct the subgroup analyses to determine the effects on various dosages, various courses of treatment, various medicine combinations, various types of cerebral hemorrhage, various course of the disease and various hemorrhage sites on the results if the data are available.

5) Assessment of reporting biases

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

Confidence in cumulative evidence

The strength of the body of evidence in this review will be assessed into high, moderate, low or very low, four levels according to the Grading of Recommendations Assessment, Development and Evaluation system[38] by GRADEpro software.

DISCUSSION

Apart from basic management, the internal medical treatment condition of ICH is unoptimistic as a result of the lack of sufficient evidence. Neuroprotective agents that was developed based on the specific pathological mechanism has the potential benefit for ICH treatment.[9] Edaravone is widely used in China even mentioned in the Chinese guidelines for acute intracerebral hemorrhage management[39] as previous meta-analyses showed edaravone was only effective in

improving neurological impairment for ICH patients.[26 27]

There are still some confusion for both clinical physicians and research fellows. Although free radical injury occurs in the pathological process of both ICH and AIS, it may be induced at different time-point. Edaravone acting as free radical scavenger was effective for AIS with time window. Therefore, the time-window for initiating edaravone, the dosage and duration of edaravone in ICH treatment are deserved to be studied. Beyond that, the neurological deficits improvement is the surrogate outcome when it comes to the assessment of specific treatment of stroke, and it lacks in robust support strength. Death and functional status after the long-term follow-up measured with mRS, GOS, and BI should be the most important outcomes for stroke patients especially in the evaluation of treatment efficacy. However, all of the confusion mentioned above were not reported in the previous meta-analyses as a result of the lack of reports in previous included articles.[26 27] After the new clinical reports were added in this updated systematic review and meta-analysis, we will mainly concern the primary outcome of long-term functional status and mortality for evaluation of edaravone. The anticipated limitations include the worrying quality of selected articles, the small sample size with relatively weak statistical power, and the difficulty caused by diversity between different studies. Therefore, we will keep cautious when interpreting the results, and take a critical approach when assessing the overall evidence. Conclusively speaking, our up-to-date systematic review and meta-analysis may update the evidence, providing new evidence for research fellows and guiding clinical physicians in properly treating ICH patients.

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.

Author Contributions: YG put forward the conception of the study. LDF and NL designed the study and LDF registered the protocol review in the PROSPERO database. LDF drafted the protocol and then revised by NL, SNG, CZ and YG. LDF and TTL will independently screen the potential studies, and then, QYY and PJ will extract data. LDF and NL will independently assess the risk of bias of the included studies. YG will arbitrate any disagreements during the review. LDF will perform the data synthesis. All authors have read and approved the final submitted version of this protocol.

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Figure 1: Flow diagram of the study selection process. ICH, intracerebral hemorrhage.

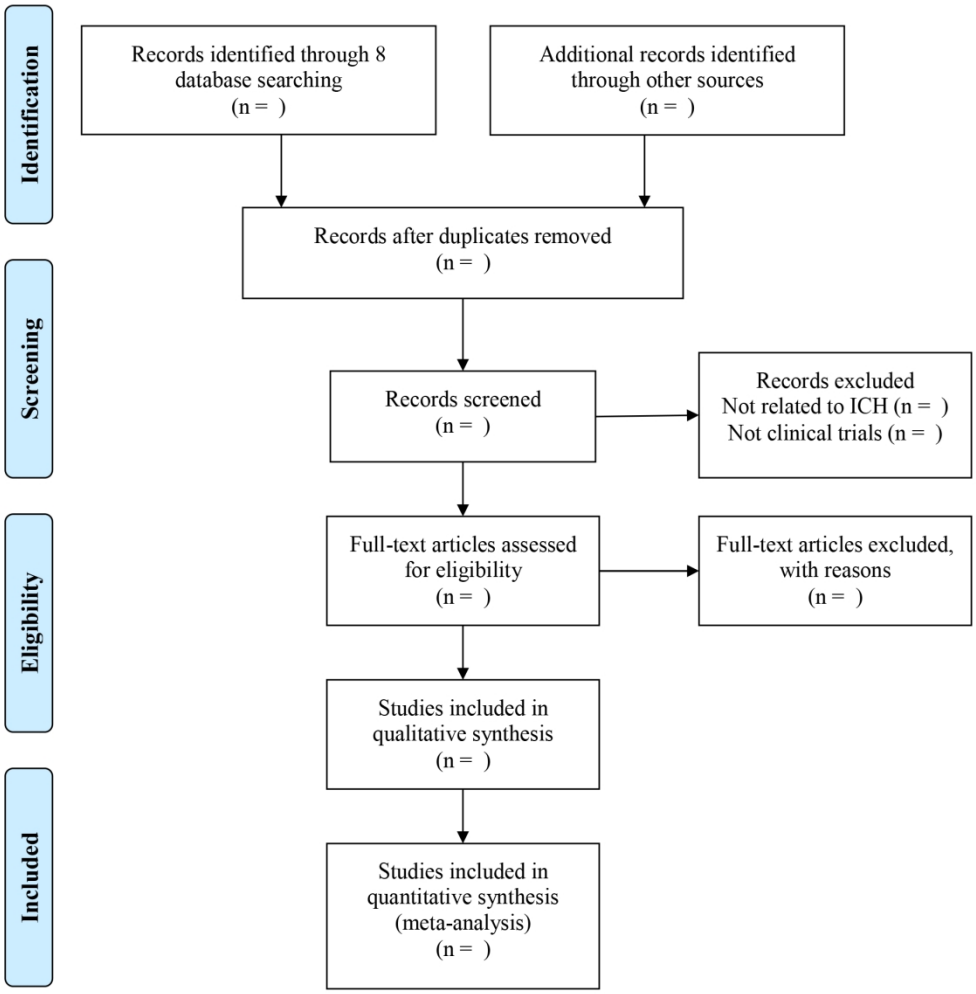

Figure 1: Flow diagram of the study selection process. ICH, intracerebral hemorrhage.

Appendix 1. Search Strategy Example: MEDLINE search

No	Search items
1	Cerebral Hemorrhage
2	Hemorrhage, Cerebrum
3	Cerebrum Hemorrhage
4	Cerebrum Hemorrhages
5	Hemorrhages, Cerebrum
6	Cerebral Parenchymal Hemorrhage
7	Cerebral Parenchymal Hemorrhages
8	Hemorrhage, Cerebral Parenchymal
9	Hemorrhages, Cerebral Parenchymal
10	Parenchymal Hemorrhage, Cerebral
11	Parenchymal Hemorrhages, Cerebral
12	Intracerebral Hemorrhage
13	Intracerebral Haemorrhage
14	Hemorrhage, Intracerebral
15	Hemorrhages, Intracerebral
16	Intracerebral Hemorrhages
17	Hemorrhage, Cerebral
18	Cerebral Hemorrhages
19	Hemorrhages, Cerebral
20	Brain Hemorrhage, Cerebral
21	Brain Hemorrhages, Cerebral
22	Cerebral Brain Hemorrhage
22	Cerebral Brain Hemorrhages
23	Hemorrhage, Cerebral Brai
24	Hemorrhages, Cerebral Brain
25	**1 OR 2-24**
26	Edaravone
27	Norantipyrine
28	Norphenazone
29	Edarabone
30	1-Phenyl-3-methyl-5-pyrazolone
31	1 Phenyl 3 methyl 5 pyrazolone
32	3-Methyl-1-phenyl-2-pyrazolin-5-one
33	3 Methyl 1 phenyl 2 pyrazolin 5 one
34	MCI 186
35	MCI-186
36	MCI186
37	Radicava
38	Phenylmethylpyrazolone
39	**26 OR 27-38**
40	Randomized controlled trial
41	Controlled clinical trial
42	Randomized
43	Placebo
44	randomly
45	**40 OR 41 OR 42 OR 43 OR 44**

46	**25 AND 39 AND 45**

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	3, 4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, 8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	8

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5, 6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8, 9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9, 10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	10

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

BMJ Open

Efficacy and Safety of Edaravone for Acute Intracerebral Haemorrhage: Protocol for a Systematic Review and Meta-Analysis

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Efficacy and Safety of Edaravone for Acute Intracerebral Haemorrhage: Protocol for a Systematic Review and Meta-Analysis

Author:

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ABSTRACT

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

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. All randomized controlled trials that (a) compared edaravone was compared with placebo, no treatment, and (b) compared edaravone plus routine treatment or co-intervention with routine treatment or co-intervention for treating acute ICH will be included. Mortality and long-term dependency will be the primary outcomes to be evaluated. 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 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.

ARTICLE SUMMARY

Strengths and limitations of this study

1) Well-recognized approach for conducting and reporting systematic reviews and meta-analysis will be followed (Cochrane handbook).
2) New trials published in recent eight years will be added in this updated systematic review and meta-analysis and the efficacy and safety of edaravone for treating intracerebral hemorrhage will be comprehensively assessed.
3) Long-term functional status and mortality will be mainly focused on as the primary outcomes in this review for the evaluation of edaravone.
4) Due to the evaluation of various time-points, dosages and duration of edaravone treatments, the findings are likely

to be heterogeneous.

5) Since different scales were used for outcome assessment, a pooled analysis of all included studies could be challenging.

Word count: 2550

INTRODUCTION

As the second most common type of stroke, nontraumatic intracerebral haemorrhage (ICH) affects 18.8% to 47.6% individuals across different races.[1-3] 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.[4 5] Though there have been significant advances in the detection and management of ICH, the clinical outcomes are still not encouraging.[5 6] Given that ICH is life-threatening and can lead to higher mortality and more severe disability compared to ischemic stroke, it is considered to be the most dangerous subtype of stroke.[7] Nearly 40% and 54% of the patients will die within the first month and first year, respectively after the onset of ICH.[8] 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 specific recommend effective internal medical treatment for ICH. Neuroprotection of the surrounding brain tissue from the degenerative effects of the hematoma is a suggested approach,[9] which is yet to be validated.

Pathological mechanisms underlying ICH are commonly categorized into (a) primary injury which refers to a direct injury caused by mass effect of the hematoma or by neurovascular disruption, and (b) secondary injury that involves in the cascade events triggered by the primary injury and its metabolites.[7] The coagulation cascade (especially thrombin), hemoglobin breakdown products, inflammation and free radicals all contributed to ICH-induced injury.[10] 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.[11]

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger[12-16] that was initially approved for treating acute ischemic stroke (AIS) in Japan.[17 18] 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 multiple effect, such as anti-inflammatory and anti-apoptotic mechanisms, attenuating ICH-induced brain edema and oxidative injury, reducing iron- and thrombin-induced brain injury and so on.[19-21] Additionally, edaravone is reported to demonstrate obvious neuroprotective effects in ICH patients and it has been widely used in the clninic.[17 22 23] 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 dosage, and duration of treatment. Basic studies showed the dosage of edaravone for ICH was higher than that for AIS, indicating the neuroprotective effects of edaravone is dose-dependent.[24 25 19 20] However, the dosage of edaravone for ICH treatment in previous systematic review and meta-analysis was similar to that for AIS.[26] Moreover, these previous studies only showed edaravone alleviating neurological function deficits,[26 27] while its effect on survival or dependency at the end of long-term follow-up were not reported. Over the past eight years, emerging evidence from several randomized controlled trials (RCTs) suggested that edaravone may be effective in treating ICH by improving the activity of daily living as well as no increase in mortality and incidence of adverse effects.[28-30] The common adverse effects associated with the use of edaravone include mild impairment of kidney function, mild impairment of liver function, skin irritation, and arrhythmia.[31 32] What's more, edaravone is a relatively expensive drug, costing approximately 600 to 860 USD for one standard course of treatment per stroke patient in China.[26] It is worth noting that despite more than 200 trials have been reported in the last eight years, the current status of edaravone as a therapeutic agent for ICH treatment remains controversial, which warrants a systematic review and meta-analysis. Under the urgent circumstances, we are decided to perform this updated systematic review and meta-analysis to obtain the conclusive evidence of edaravone for ICH treatment.

Objectives

This updated systematic review and meta-analysis aims at systematically analyzing all 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 in making an informed choice regarding treatment for ICH.

METHODS AND ANALYSIS

Our protocol of systematic review and meta-analysis was registered in the International Prospective Register of Systematic Review (PROSPERO), and the registration number was CRD42019147801 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019147801). This protocol was performed following the reporting items listed in the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P),[33 34] which was established aiming at facilitating the preparation and reporting of a robust protocol for the systematic review and meta-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. The anticipated start date of this study is 23/04/2020.

Eligibility criteria

1. Types of studies

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

2. Types of participants

Adult patients with acute ICH (within seven days) as diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) will be included according to a guideline for healthcare professionals from the American Heart

Association/American Stroke Association[9] will be included. There will be no restrictions in terms of the patients' age, gender, race, education or economic status. Patients with traumatic hemorrhagic stroke, primary intraventricular haemorrhage, and subarachnoid haemorrhage will be excluded.

3. Types of intervention

We will mainly focus on the intervention where edaravone was compared with placebo or no treatment. Additionally, routine treatments or co-interventions will also be allowed when the routine treatment or co-interventions are administered equally to all intervention groups of a trial. However, there will be no restriction on the course of treatment.

4. 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 report numerical data on one or more of the following outcomes will be considered.

4.1 *Primary outcome*

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

4.2 *Secondary outcomes*

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

4.3 *Safety outcome*

Adverse effects of edaravone including impairment of kidney function, impairment of liver function, skin irritation, nausea, to name a few, will be evaluated.

Search strategy

We will conduct the comprehensive electronic searches of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Given that edaravone is widely used in China, we will search the following Chinese databases: China National Knowledge Infrastructure (CNKI), 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.[35] We will develop the search strategy for MEDLINE (see supplementary material 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:

1) World Health Organization International Clinical Trials Registry Platform (ICTRP),
2) ClinicalTrials.gov,
3) The United Kingdoms' ISRCTN registry (ISRCTN),
4) Chinese Clinical Trial Registry (ChiCTR),
5) Australia and New Zealand Clinical Trials Registry (ANZCTR),
6) The Netherlands Trial Register (NTR),
7) German Clinical Trials Register (DRKS),
8) Japan Primary Registries Network (JPRN),
9) Clinical Trials Registry – India (CTRI),
10) Iranian Registry of Clinical Trials (IRCT),
11) Sri Lanka Clinical Trials Registry (SLCTR).

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

Screening and selection

Duplicate articles will be removed after identifying them by database searching. Two review authors (LDF, TTL) will independently screen the articles for titles and abstracts of articles 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 obviously 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 had not been 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 (QYY, PJ) will independently extract data on methods, patients, interventions, outcomes and results from 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.[35]

Quality assessment

The methodological quality assessment of the eligible studies will be independently conducted by two reviewers (LDF, NL) for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[35]. They will resolve any disagreements 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 with effort. We will provide information from the study report together with a justification for our judgment, in the 'risk of bias' tables.

Data synthesis and management

1) Measures of treatment effect

We plan to summarize the data using risk ratio (RR) calculations and 95% confidence intervals (CIs) for dichotomous outcomes, and mean differences (MDs) with 95% CIs for continuous outcomes in the final analysis. We will calculate standardized mean differences (SMDs) 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 e-mail or telephone to obtain the missing data or information which was not clearly described. In case the missing data is unavailable, intention-to-treat and sensitivity analyses will be performed to address the potential impact of the missing data.[36 37] The impact of missing data will be discussed if necessary.

3) Assessment of heterogeneity and data synthesis

Statistical heterogeneity amongst 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 synthesize the data, and if it is between 25%-75%, we will estimate the sources of the heterogeneity. If the statistical heterogeneity is explained successfully by sensitive analysis or subgroup analysis (i.e., I^2 is less than 25%), we will also use

the fixed-effect model to synthesize the data, otherwise, a random-effects model will be applied. Data will not be synthesized if there is a significant level of statistical heterogeneity amongst the trials (i.e., I^2 is greater than 75%) that cannot be explained or handled by subgroup analysis. All statistical analyses will be performed using Review Manager 5.3 (The Cochrane Collaboration) software.

4) Analysis of subgroups or subsets

We will conduct subgroup analyses to determine the effects of various dosages of edaravone, courses of treatment, drug combination, types of cerebral haemorrhage, courses of disease and haemorrhage sites on the results, if the data are available.

5) Assessment of reporting biases

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

Confidence in cumulative evidence

The strength of the body of evidence in this review will be categorized as high, moderate, low or very low according to the Grading of Recommendations Assessment, Development and Evaluation system[38] 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.[9] Edaravone is widely used in China even mentioned in the Chinese guidelines for acute intracerebral haemorrhage management[39] as previous meta-analyses have shown edaravone to be effective only in improving neurological impairment for ICH patients.[26 27]

Free radical injury is involved in the pathological process of both ICH and AIS, though it may be induced at different time-points in the two conditions. Edaravone acting as a free radical scavenger is effective in case of AIS when administered during a specific time window. Therefore, the optimal time for initiating edaravone treatment, the proper dosage and duration of treatment in case of 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 it 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, all of the confusion mentioned above were not reported in the previous meta-analyses due to the lack of reports in previously included articles.[26 27] After adding new clinical reports in 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 review has some potential limitations. Various time-points, dosage 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 is available. Additionally, we will

interpret the results with caution, and take a critical approach when assessing the overall evidence.

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

Author Contributions: YG put forward the conception of the study. LDF and NL designed the study. LDF drafted the protocol and then it was revised by NL, SNG, CZ and YG. LDF and TTL will independently screen the potential studies, and then, LDF and NL will independently assess the risk of bias of the included studies. YG will arbitrate any disagreements during the review. QYY and PJ will extract data. LDF will perform data synthesis. All authors have read and approved the final submitted version of this protocol.

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

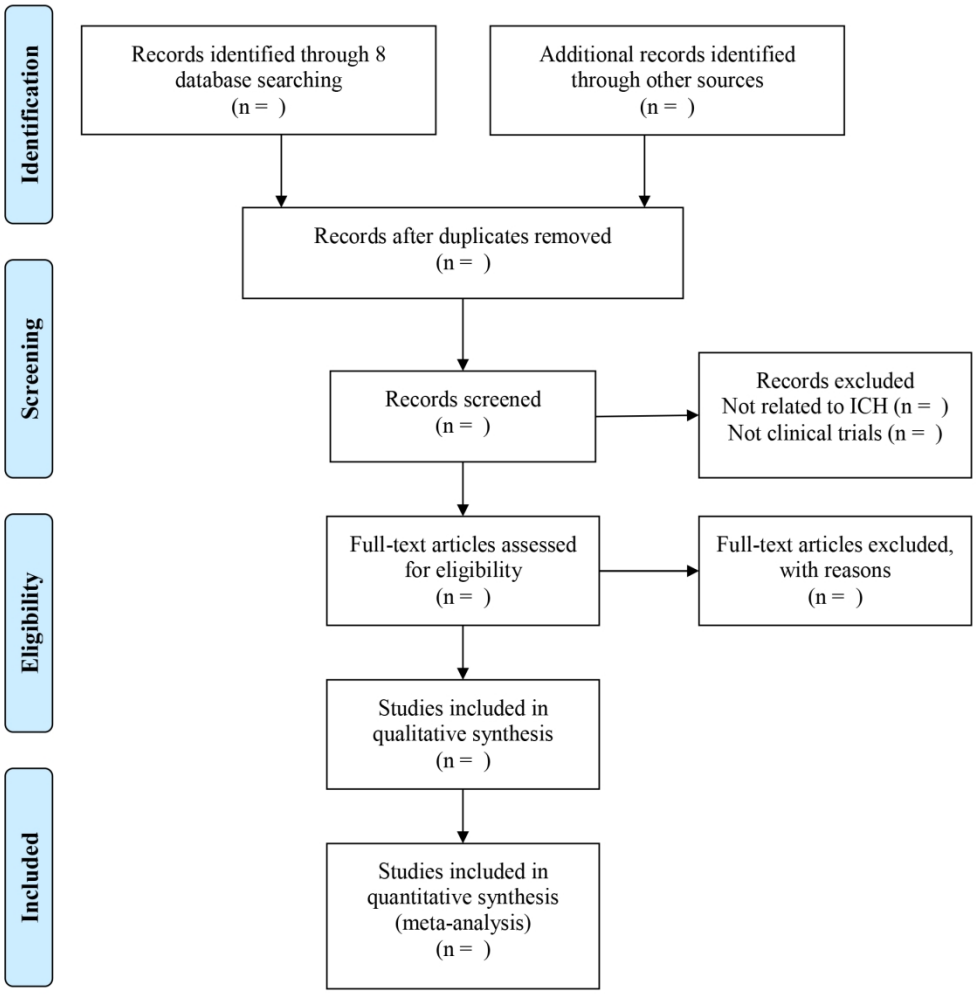

Figure 1: Flow diagram of the study selection process. ICH, intracerebral haemorrhage.

Appendix 1. Search Strategy Example: MEDLINE search

No	Search items
1	Cerebral Hemorrhage
2	Hemorrhage, Cerebrum
3	Cerebrum Hemorrhage
4	Cerebrum Hemorrhages
5	Hemorrhages, Cerebrum
6	Cerebral Parenchymal Hemorrhage
7	Cerebral Parenchymal Hemorrhages
8	Hemorrhage, Cerebral Parenchymal
9	Hemorrhages, Cerebral Parenchymal
10	Parenchymal Hemorrhage, Cerebral
11	Parenchymal Hemorrhages, Cerebral
12	Intracerebral Hemorrhage
13	Intracerebral Haemorrhage
14	Hemorrhage, Intracerebral
15	Hemorrhages, Intracerebral
16	Intracerebral Hemorrhages
17	Hemorrhage, Cerebral
18	Cerebral Hemorrhages
19	Hemorrhages, Cerebral
20	Brain Hemorrhage, Cerebral
21	Brain Hemorrhages, Cerebral
22	Cerebral Brain Hemorrhage
22	Cerebral Brain Hemorrhages
23	Hemorrhage, Cerebral Brai
24	Hemorrhages, Cerebral Brain
25	**1 OR 2-24**
26	Edaravone
27	Norantipyrine
28	Norphenazone
29	Edarabone
30	1-Phenyl-3-methyl-5-pyrazolone
31	1 Phenyl 3 methyl 5 pyrazolone
32	3-Methyl-1-phenyl-2-pyrazolin-5-one
33	3 Methyl 1 phenyl 2 pyrazolin 5 one
34	MCI 186
35	MCI-186
36	MCI186
37	Radicava
38	Phenylmethylpyrazolone
39	**26 OR 27-38**
40	Randomized controlled trial
41	Controlled clinical trial
42	Randomized
43	Placebo
44	randomly
45	**40 OR 41 OR 42 OR 43 OR 44**

46	**25 AND 39 AND 45**

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	3, 4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, 8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	8

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5, 6
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8, 9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9, 10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9, 10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	10

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

BMJ Open

Efficacy and Safety of Edaravone for Acute Intracerebral Haemorrhage: Protocol for a Systematic Review and Meta-Analysis

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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 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 eight 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 randomized controlled trials that (a) compared edaravone with placebo or no treatment, and (b) compared edaravone plus routine treatment or co-intervention with routine treatment or co-intervention 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 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.

ARTICLE SUMMARY

Strengths and limitations of this study

1) A well-recognized approach for conducting and reporting systematic reviews and meta-analysis will be followed (Cochrane handbook).
2) New trials published in the recent eight 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.
3) Long-term functional status and mortality will be mainly focused on as the primary outcomes in this review for the evaluation of edaravone.
4) Due to the evaluation of various time-points, dose and duration of edaravone treatments, the findings are likely to be heterogeneous.
5) Since different scales were used for outcome assessment, a pooled analysis of all included studies could be challenging.

INTRODUCTION

Non-traumatic intracerebral haemorrhage (ICH) is the second most common type of stroke, affecting 18.8%-47.6% of individuals across different races.[1-3] 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.[4 5] Though there have been significant advances in the detection and management of ICH, the clinical outcomes are still not encouraging.[5 6] Given that ICH is life-threatening and can lead to higher mortality and more severe disability compared to ischemic stroke, it is considered to be the most dangerous subtype of stroke.[7] Nearly 40% and 54% of the patients will die within the first month and the first year, respectively after the onset of ICH.[8] 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 hematoma is a suggested

approach,[9] which is yet to be validated.

Pathological mechanisms underlying ICH are commonly categorized into (a) primary injury which refers to a direct injury caused by mass effect of the hematoma or by neurovascular disruption, and (b) secondary injury that involves in the cascade events triggered by the primary injury and its metabolites.[7] The coagulation cascade (especially thrombin), hemoglobin breakdown products, inflammation and free radicals all contributed to ICH-induced injury.[10] 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.[11]

Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger[12-16] that was initially approved for treating acute ischemic stroke (AIS) in Japan.[17 18] 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 anti-apoptotic mechanisms, attenuating the ICH-induced brain edema and oxidative injury, as well as reducing iron- and thrombin-induced brain injury.[19-21] Additionally, edaravone is reported to demonstrate obvious neuroprotective effects in ICH patients and has been widely used in clinic.[17 22 23]

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 to AIS, treatment of ICH requires higher doses of edaravone, indicating its dose-dependent neuroprotective effects.[24 25 19 20] However, the dose of edaravone for ICH treatment in previous systematic review and meta-analysis was similar to that for AIS.[26] Moreover, these previous studies only showed edaravone alleviating neurological function deficits,[26 27] while its effect on survival or dependency at the end of long-term follow-up were not reported. Over the past eight years, emerging evidence from several randomized 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.[28-30] The common adverse effects associated with the use of edaravone include mild impairment of kidney and liver function, skin irritation, and arrhythmia.[31 32] What's more,

edaravone is a relatively expensive drug, costing approximately 600 to 860 USD for one standard course of treatment per stroke patient in China.[26] It is worth noting that despite more than 200 trials have been reported in the last eight 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 analyzing 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. It has been registered in the International Prospective Register of Systematic Review (PROSPERO), and the registration number is CRD42019147801 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019147801). This protocol was performed following the reporting items listed in the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P),[33 34] 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 23/04/2020.

Eligibility criteria

1. 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.

2. Types of participants

Adult patients with acute ICH (within seven days) diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) according to a guideline for healthcare professionals from the American Heart Association/American Stroke Association[9] 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.

3. 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 co-interventions with edaravone were administered equally to all groups, will also be included. However, there will be no restriction on the course of treatment.

4. 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.

4.1 *Primary outcome*

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 grade 3 to 6, GOS grade 1 to 3, or BI less than or equal to 60.

4.2 *Secondary outcomes*

The secondary outcomes will include: (1) improvement of neurological impairment assessed using clinical scales including the National Institute of Health Stroke Scale (NIHSS), Canadian Neurological Scale (CNS), European

Stroke Scale (ESS), Scandinavian Stroke Scale (SSS), Modified Edinburgh-Scandinavian Stroke Scale (MESSS) and other related scales, (2) the total efficiency rate including cure rate, obvious effective rate, and effective rate, and (3) reduction in the hematoma volume.

4.3 *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 (CENTRAL). Given that edaravone is widely used in China, we will search the following Chinese databases: China National Knowledge Infrastructure (CNKI), 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.[35] We will develop the search strategy for MEDLINE (see supplementary material 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:

- World Health Organization International Clinical Trials Registry Platform (ICTRP),
- ClinicalTrials.gov,
- The United Kingdoms' ISRCTN registry (ISRCTN),
- Chinese Clinical Trial Registry (ChiCTR),
- Australia and New Zealand Clinical Trials Registry (ANZCTR),
- The Netherlands Trial Register (NTR),
- German Clinical Trials Register (DRKS),
- Japan Primary Registries Network (JPRN),

- Clinical Trials Registry – India (CTRI),
- Iranian Registry of Clinical Trials (IRCT),
- Sri Lanka Clinical Trials Registry (SLCTR).

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 (LDF, TTL) 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 (QYY, 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.[35]

Quality assessment

The methodological quality assessment of the eligible studies will be independently conducted by two reviewers

(LDF, NL) for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[35]. 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 judgment, in the 'risk of bias' tables.

Data synthesis and management

1) Measures of treatment effect

We plan to summarize the data using risk ratio (RR) calculations and 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes in the final analysis. We will calculate standardized mean differences (SMDs) 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 e-mail or telephone to obtain the missing data or information which was not clearly described. In case the missing data is unavailable, intention-to-treat and sensitivity analyses will be performed to address the potential impact of the missing data,[36 37] which will then be discussed if necessary.

3) Assessment of heterogeneity and data synthesis

Statistical heterogeneity amongst 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 synthesize the data, and if it is between 25%-75%, we will estimate the sources of the heterogeneity. If the statistical heterogeneity is explained successfully by sensitive analysis or subgroup analysis (i.e., I^2 is less than 25%), we will also use the fixed-effect model to synthesize the data. Otherwise, a random-effect model will be applied. Data will not be synthesized if there is a significant level of statistical heterogeneity amongst the trials (i.e., I^2 is greater than 75%) that cannot be explained or handled by subgroup analysis. All statistical analyses will be performed using Review Manager 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 milligrams per day, 60 milligrams per day, and more than 60 milligrams per 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 SMASH-U (Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined) etiologic 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 ten or more trials are included per comparison.

Confidence in cumulative evidence

The strength of the body of evidence in this review will be categorized as high, moderate, low or very low according to the Grading of Recommendations Assessment, Development and Evaluation system[38] 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.[9] Edaravone is widely used in China, and is even mentioned in the Chinese guidelines for acute ICH management.[39] Previous meta-analyses have shown edaravone to be effective only in improving neurological impairment for ICH patients.[26 27]

Free radical injury is involved in the pathological process of both ICH and AIS, though it may be induced at different time-points 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 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.[26 27] 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 time-points, 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.

Author Contributions: YG put forward the conception of the study. LDF and NL designed the study. LDF drafted the protocol and then it was revised by NL, SNG, CZ and YG. LDF and TTL will independently screen the potential studies, and then, LDF and NL will independently assess the risk of bias of the included studies. YG will arbitrate any disagreements during the review. QYY and PJ will extract data. LDF will perform data synthesis. All authors have read and approved the final submitted version of this protocol.

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References:

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Figure Legend

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

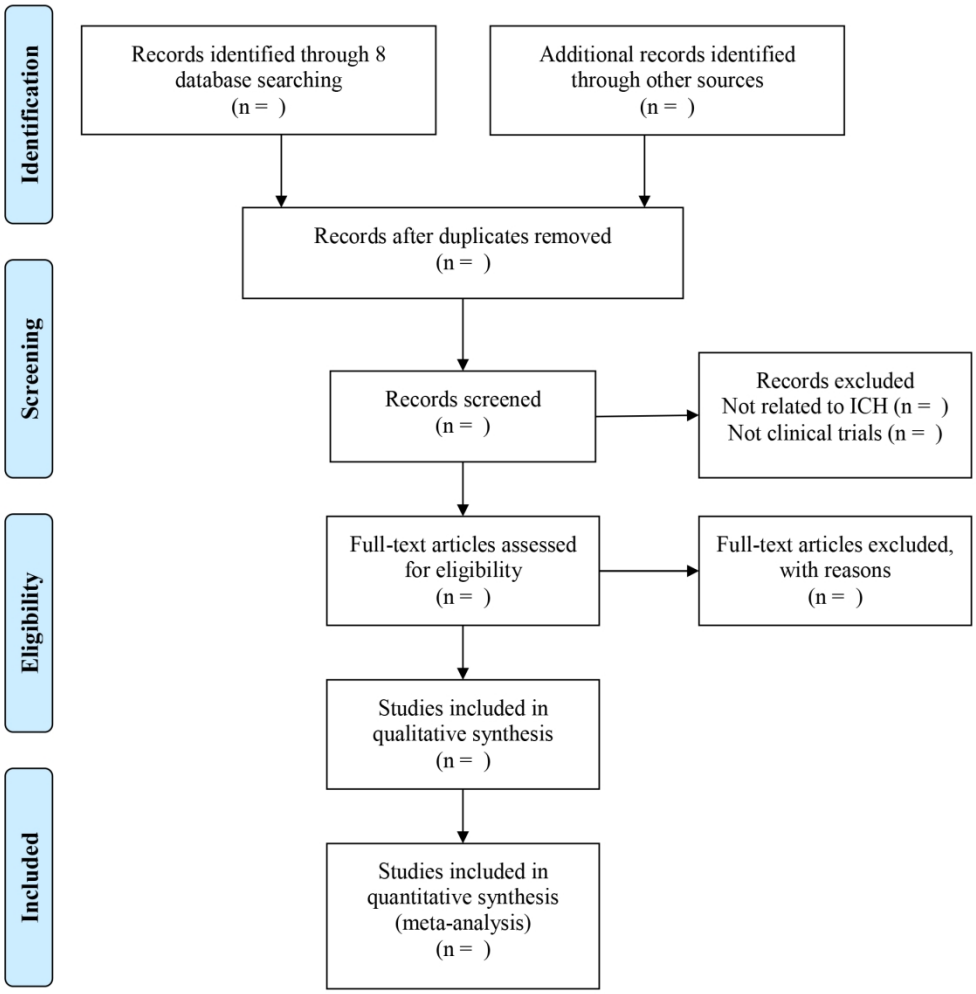

Figure 1: Flow diagram of the study selection process. ICH, intracerebral haemorrhage.

Appendix 1. Search Strategy Example: MEDLINE search

No	Search items
1	Cerebral Hemorrhage
2	Hemorrhage, Cerebrum
3	Cerebrum Hemorrhage
4	Cerebrum Hemorrhages
5	Hemorrhages, Cerebrum
6	Cerebral Parenchymal Hemorrhage
7	Cerebral Parenchymal Hemorrhages
8	Hemorrhage, Cerebral Parenchymal
9	Hemorrhages, Cerebral Parenchymal
10	Parenchymal Hemorrhage, Cerebral
11	Parenchymal Hemorrhages, Cerebral
12	Intracerebral Hemorrhage
13	Intracerebral Haemorrhage
14	Hemorrhage, Intracerebral
15	Hemorrhages, Intracerebral
16	Intracerebral Hemorrhages
17	Hemorrhage, Cerebral
18	Cerebral Hemorrhages
19	Hemorrhages, Cerebral
20	Brain Hemorrhage, Cerebral
21	Brain Hemorrhages, Cerebral
22	Cerebral Brain Hemorrhage
22	Cerebral Brain Hemorrhages
23	Hemorrhage, Cerebral Brai
24	Hemorrhages, Cerebral Brain
25	**1 OR 2-24**
26	Edaravone
27	Norantipyrine
28	Norphenazone
29	Edarabone
30	1-Phenyl-3-methyl-5-pyrazolone
31	1 Phenyl 3 methyl 5 pyrazolone
32	3-Methyl-1-phenyl-2-pyrazolin-5-one
33	3 Methyl 1 phenyl 2 pyrazolin 5 one
34	MCI 186
35	MCI-186
36	MCI186
37	Radicava
38	Phenylmethylpyrazolone
39	**26 OR 27-38**
40	Randomized controlled trial
41	Controlled clinical trial
42	Randomized
43	Placebo
44	randomly
45	**40 OR 41 OR 42 OR 43 OR 44**

46	**25 AND 39 AND 45**

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	3, 4

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9, 10
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	8

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5-7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6, 7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8, 9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9, 10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9, 10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	10

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10, 11