Clinical effects and safety of edaravone in treatment of acute ischaemic stroke: A meta-analysis of randomized controlled trials

Chongyue Chen MD¹ | Mingkai Li PhD² | Liling Lin MD³ | Shuying Chen MD, PhD³ | Yongru Chen MD¹ | Liekai Hong MD⁴

¹Department of Emergency Intensive Care Unit, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
²Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, Guangdong, China
³Department of Neurology, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
⁴Department of Cardiovascular, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China

Correspondence
Liekai Hong, MD, Department of Cardiovascular, The First Affiliated Hospital of Shantou University Medical College, 57 Changping Road, Shantou 515041, Guangdong, China.
Email: hongliekai@163.com

Funding information
The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Abstract
What is known and objective: Edaravone is a new antioxidant and hydroxyl radical scavenger. Although there is evidence that it improves clinical outcomes of patients with acute ischaemic stroke (AIS), it is not yet widely accepted for treatment of AIS in Western countries. We further investigated the efficacy and safety of edaravone through this meta-analysis of randomized controlled clinical trials (RCTs).

Method: Pubmed, Embase, Web of Science and Cochrane Library were screened up to December 2020 for original articles from SCI journals that published in English. RCTs that compared edaravone versus placebo or no intervention in adult patients and reported the efficacy or safety of edaravone were regarded as eligible. Mortality was regarded as the primary outcome and the improvement of neurological impairment was regarded as the secondary outcome. Safety evaluation was conducted according to the incidence of adverse events. Review Manager 5.3 was employed to perform the assessment of the risk of bias and data synthesis. The Cochrane risk of bias tool for randomized controlled trials was employed to assess the risk of bias.

Results and discussion: Seven randomized controlled trials with 2069 patients were included. For the incidence of mortality, the pooled RR for studies that evaluated edaravone after three-month follow-up was 0.55 (95% CI, 0.43-0.7, \( I^2 = 0 \), \( P < 0.01 \)). The pooled RR for improvement of neurological impairment at the three months follow-up was 1.54 (95% CI, 1.27-1.87, \( I^2 = 0 \) ) in four RCTs. On subgroup analysis of studies that were conducted in Asia, the RR was 1.56 (95% CI, 1.27-1.90, \( I^2 = 0 \% \); \( P < 0.01 \)); the pooled RR for studies that conducted in Europe was 1.32 (95% CI, 0.64-2.72; \( P = 0.45 \)); the pooled RR for studies that used edaravone for two weeks was 1.42 (95% CI, 1.10 to 1.83, \( I^2 = 0 \% \); \( P < 0.01 \)); the pooled RR for studies that used edaravone for one week was 1.64 (95% CI, 1.24-2.16, \( I^2 = 0 \% \); \( P < 0.01 \)); the pooled RR for studies that conducted in patients with mean age equal to or over 60 years was 1.52 (95% CI, 1.24-1.87, \( I^2 = 0 \% \); \( P < 0.01 \)); and the pooled RR for studies that conducted in patients with mean age less than 60 was 1.80 (95% CI, 1.05-3.08, \( I^2 = 0 \% \); \( P = 0.03 \)). For the
incidence of any treatment-related adverse events, the pooled RR for studies that evaluated edaravone during treatment was 0.83 (95% CI, 0.51-1.34, I² = 0, P = 0.43). The difference of the incidence of any treatment-related adverse events between two groups was not statistically significant.

**What is new and conclusion:** The limited studies indicate that edaravone can improve neurological impairment with a survival benefit at three-month follow-up, regardless of the mean age and course of treatment. It is worthy of promotion in the clinical treatment of AIS in Asian countries. More well-designed RCTs with larger sample sizes are needed to determine the benefits of edaravone in patients from Western countries.

**KEYWORDS**
acutely ischaemic stroke, edaravone, efficacy and safety, meta-analysis, randomized controlled clinical trials

**1 | WHAT IS KNOWN AND OBJECTIVE**

Cerebrovascular disease is a major cause of death and disability worldwide. Acute ischaemic stroke (AIS) is the most common type of cerebrovascular disease. Despite the availability of antithrombotic drugs and endovascular treatment in most cases, AIS remains a major public health issue that poses a significant health burden. Brain ischaemia is regarded as a process of delayed neuronal cell death. Diminished cerebral blood flow triggers the “ischaemic cascade” that results in intracellular calcium overload, an increased number of abnormal free radicals and cytotoxic oedema to facilitate cell destruction. To interrupt the process that ischaemic neurons undergo as part of the ultimate common pathway of cell death remains a hot topic of neuroprotection.

As the first free radical scavenger for acute ischaemic stroke, edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) is produced by Mitsubishi Tanabe Pharma Corporation (Japan). Edaravone was approved for sale in Japan in 2001 and has been widely accepted for clinical use in Japan, China and India. Edaravone was first regarded to express a favourable performance in animal models of stroke in the late 1980s. There exist three underlying antioxidative mechanisms of edaravone. Firstly, edaravone was reported to inhibit both lipid-soluble and water-soluble peroxyl radical-induced peroxidation systems. Secondly, non-enzymatic lipid peroxidation and lip-oxygenase pathways are halted by the utilization of edaravone. Lastly, quenching hydroxyl radical (OH) can suppress the OH-dependent and OH-independent lipid peroxidation. Since edaravone expresses powerful antioxidative performance and it was validated in clinical application, the Japanese Guidelines for the Management of Stroke in 2009 suggested edaravone for AIS as a grade B recommendation. Though edaravone is widely accepted in many Asian countries, it has not been approved for clinical application in Western countries. Although a previous meta-analysis has confirmed the favourable outcomes of edaravone applied in acute stroke patients, the quality of included studies of edaravone for acute stroke was generally poor. Most of the included trials were conducted in Asia and only focused on the short-term improvement of neurological deficit. Due to the reported liver and kidney dysfunction associated with edaravone, its safety should also be carefully taken into consideration. To further determine efficacy and safety of edaravone, we performed a meta-analysis of randomized controlled trials (RCTs) to evaluate its clinical effect of edaravone in treatment of AIS.

**2 | METHODS**

**2.1 | Search strategy**

The specific search strategy is listed in Table S1. Four authorized online databases, namely Pubmed/Medline, Embase, the Web of Science, and the Cochrane Library were screened up to December 2020 utilizing the following key words: edaravone, MCI-186, stroke, brain infarct, cerebral infraction, cerebrovascular disease, brain attack.

**2.2 | Inclusion and exclusion criteria**

Original articles were considered initially eligible if they met the following criteria: (i) randomized controlled trials comparing edaravone versus placebo or no intervention in adult patients. These patients were clinically diagnosed as AIS in accordance with the WHO case definition or the Fourth National Cerebrovascular Disease Conference of China. (ii) The original articles need to be published in English and could be screened in SCI journals. The following situations were considered as the exclusion criteria: (i) studies on children or animal; (ii) when patients with transient ischaemic attacks (TIAs), intracerebral haemorrhage or subarachnoid haemorrhage were included; (iii) when patients with severe liver or renal dysfunction were included; and (iv) when patients with previous edaravone allergy were included.
2.3 | Outcomes assessed

Mortality at 3 months follow-up reported in each RCT was regarded as the primary outcome. The secondary outcome we assessed was the improvement of neurological impairment. Improvement of neurological impairment was identified with the modified Rankin Scale (mRS) grade 0-2, the evident reduction of NIH Stroke Scale (NIHSS) or the authors’ own judgements. Safety outcomes included reported adverse events. The adverse events related with edaravone were extracted from the original articles.

2.4 | Data extraction and quality assessment of the included articles

Two experienced researchers (CC and SC) were invited to screen the online databases and make preliminary selections. The eligibility and quality of each article were cautiously screened by each investigator. Two researchers then extracted the targeted data separately. Basic and technical characteristics of the included studies were summarized in our pre-designed forms. According to the criteria listed in the Cochrane Handbook for Systematic Reviews of Interventions,15 two experienced reviewers (CC, QZ) conducted the methodological quality assessment of the eligible RCTs using the Cochrane tool for assessing the risk of bias with Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK). A third reviewer (ML) was invited to assess the disagreements between the two researchers.

2.5 | Statistical analysis

2.5.1 | Measurement of outcomes

The continuous data were presented as mean ± standard deviation (SD). Review Manager 5.3 was introduced to perform the
### Table 1: Basic characteristics of the included studies

| Author   | Year | Region | Methods of randomization | Number of the patients (Tre/Con) | Mean age, y (Tre/Con) | Male, Sex % (Tre/Con) | Time window (h) | Dose range (mg/d) | Duration of treatment (d) | Duration of follow-up (d) | Evaluation criterion |
|----------|------|--------|---------------------------|----------------------------------|----------------------|----------------------|------------------|------------------|--------------------------|--------------------------|----------------------|
| Kaste    | 2013 | Europe | Unclear                   | 25/11                            | 63.5/69              | 76/72.7              | ≤24               | 12 patients: 1.52 mg/kg; 11 patients: 3.04 mg/kg | 3                        | 90                       | mRS/NIHSS/BI            |
| Li       | 2019 | China  | Unclear                   | 48/48                            | 60.5/62.5            | 52.1/60.4            | ≤48               | 60               | 14                       | 14                       | NIHSS/ADL             |
| Miyaji   | 2015 | Japan  | Unclear                   | 1129/313                         | 73.2/76.9            | 55.8/56.9            | ≤24               | 60               | 7                        | 90                       | mRS                  |
| Otomo    | 2003 | Japan  | Random Table              | 125/125                          | 66.3/66.1            | 65.6/67.2            | ≤72               | 60               | 14                       | 365                      | mRS                  |
| Sharma   | 2011 | India  | Random Table              | 25/25                            | 58.1/56              | 64/60                | ≤72               | 60               | 14                       | 90                       | mRS/BI                |
| Sun      | 2019 | China  | Random Table              | 65/65                            | 52.4/51.3            | 56.9/61.5            | Unclear           | 60               | 14                       | 14                       | NIHSS/ADL/FMA          |
| Zheng    | 2015 | China  | Random Table              | 35/30                            | 63.4/59.8            | 57.1/53.3            | ≤24               | 60               | 14                       | 14                       | NIHSS/BI              |

### Table 2: Quality assessment of the included studies

| Author   | Year | Selection bias | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias |
|----------|------|----------------|------------------|----------------|----------------|----------------|------------|
|          |      | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
| Kaste    | 2013 | Low risk       | Low risk         | Low risk       | Low risk       | Low risk       | Low risk   | Unclear risk |
| Li       | 2019 | Low risk       | Low risk         | Low risk       | Low risk       | Low risk       | Low risk   | Unclear risk |
| Miyaji   | 2015 | Low risk       | Low risk         | Low risk       | Low risk       | Low risk       | Low risk   | Unclear risk |
| Otomo    | 2003 | Low risk       | Low risk         | Low risk       | Low risk       | Low risk       | Low risk   | Low risk     |
| Sharma   | 2011 | Low risk       | Unclear risk     | Low risk       | Low risk       | Low risk       | Low risk   | Unclear risk |
| Sun      | 2019 | Low risk       | Low risk         | Unclear risk   | Low risk       | Low risk       | Low risk   | Unclear risk |
| Zheng    | 2015 | Low risk       | Unclear risk     | Low risk       | Low risk       | Low risk       | Low risk   | Unclear risk |
statistical analysis. The relative risk (RR) and 95% CI that associated with the candidate outcomes in each group were pooled utilizing the DerSimonian and Laird random-effects or fixed model according to the potential heterogeneity.\textsuperscript{16}

2.5.2 Assessment of heterogeneity

We judged the heterogeneity by the $\chi^2$ statistic presented in the forest plots generated by Review Manager 5.3. An $I^2 > 50\%$ was regarded as a threshold for determining substantial statistical heterogeneity.\textsuperscript{17}

2.5.3 Data synthesis

DerSimonian and Laird random-effects model and Mantel-Haenszel (M-H) methods were applied if there was substantial statistical heterogeneity. Otherwise, a fixed-effects model was the preferred choice to perform meta-analysis. Funnel plots were generated by Review Manager 5.3 for the evaluation of publication bias of the included studies (Figure S1). A $P < 0.05$ was considered statistically significant.

3 RESULTS

3.1 Characteristics and the quality of the retrieved studies

A total of 1369 records were retrieved utilizing our primary search strategies. 452 articles were identified after duplications removed. After excluding commentaries, conference abstracts, reviews and meta-analyses, non-English articles, non-SCI studies, and studies not related to the application of edaravone or MCI-186 in the treatment
of stroke, brain infarct, cerebral infarction, cerebrovascular disease or brain attack, 25 articles were downloaded for further selection. Finally, 7 studies were included for this meta-analysis. The flow diagram of the study selection is presented in Figure 1. Table 1 shows the characteristics of these studies. A multicentre, double-blind, placebo-controlled RCT enrolled AIS patients from Europe. The other six RCTs was conducted in Asia. 269 subjects (mean age, 70.1 years; 58.0% male) were included, of whom 1425 patients (mean age, 70.6 years; 57.1% male) were exposed to edaravone. The other 617 patients (mean age, 69.1 years; 60.0% male) were regarded as the control group. All RCTs focused on the comparison of edaravone plus conventional therapy with routine treatment alone. Three RCTs investigated patients with a treatment time window within 24 h, and three RCTs investigated patients with stable vital signs who were admitted to hospitals during 24-72 hours after the onset of stroke. Five RCTs investigated patients treated with edaravone for two weeks and the other two RCTs included patients treated with edaravone for one week. Four RCTs evaluated outcome at the long-term follow-up, namely three months or later. The other three RCTs made an assessment at two weeks follow-up. The detailed quality assessment of the included studies is presented in Table 2 and Figure 2.

### 3.2 Outcome evaluation

#### 3.2.1 Mortality

Three RCTs including 1720 patients reported the mortality at three months follow-up. In the control group, 83 (18.4%) deaths occurred among 451 participants. Regarding the edaravone group, at three months follow-up 153 (12.1%) patients died. The results showed that the \( I^2 \) value and \( P \) value for evaluation of mortality were 0.01 and 0.1, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 3, a significant reduction of mortality was observed in the edaravone group than in the control group (RR = 0.55, 95% CI, 0.43-0.70, \( I^2 = 0\% \); \( P < 0.01 \)). Figure S1 shows that there was no evidence of publication bias for assessment of the mortality at three-month follow-up.

#### 3.2.2 Improvement of neurological impairment

Four RCTs including 1778 patients evaluated the improvement of neurological impairment according to the authors’ judgements at three-month follow-up. For comparison of outcome, they divided patients into two groups with favourable (mRS0-2) and poor (mRS3-6) outcomes. In the control group, 105 (22.2%) patients exhibited neurological improvement among 474 participants. Regarding the edaravone group, at three-month follow-up 355 (27.2%) patients reported neurologic improvement. The results showed that the \( I^2 \) value and \( P \) value for evaluation of improvement of neurological impairment were 0.01 and 0.64, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 4, a significant improvement of neurological impairment was observed in the edaravone group than in the control group (RR = 1.54, 95% CI, 1.27-1.87, \( I^2 = 0\% \); \( P < 0.01 \)). Subgroup analysis of the patients from different continents included three studies that assessed the efficacy of edaravone in Asian patients (RR, 1.56; 95% CI, 1.27-1.87; \( I^2 = 0\% \); \( P < 0.01 \)). One study that evaluated edaravone in European patients (RR, 1.32; 95% CI, 0.64-2.72; \( P = 0.45 \)) (Figure 5A). The second subgroup analysis was based on the duration of the treatment of edaravone, namely 1 week and 2-week treatment. The pooled RR for patients treated with edaravone for 2 weeks was 1.42 (95% CI, 1.13-1.77).
(A) Study or Subgroup  |  Experimental Events  |  Control Total Events  |  Total Weight  |  Risk Ratio M.H. Fixed, 95% CI
---|---|---|---|---
2.4.1 Asia  |  |  |  |  
Miyaj 2015  | 259  | 1129  | 43  | 313  | 51.3%  | 1.67 [1.24, 2.25]  
Otomo 2003  | 63  | 125  | 47  | 125  | 35.8%  | 1.34 [1.01, 1.78]  
Sharma 2011  | 18  | 25  | 10  | 25  | 7.6%  | 1.80 [1.05, 3.08]  
Subtotal (95% CI)  | 1279  | 463  | 94.7%  | 1.56 [1.27, 1.90]  
Total events  | 340  | 100  |  |  
Heterogeneity: $\chi^2 = 5.55$, df = 2 ($P = 0.46$); $I^2 = 0\%$  
Test for overall effect: $Z = 4.23$ ($P < 0.0001$)

2.4.2 Europea  |  |  |  |  
Kaste 2013  | 15  | 25  | 5  | 11  | 5.3%  | 1.32 [0.64, 2.72]  
Subtotal (95% CI)  | 25  | 11  | 5.3%  | 1.32 [0.64, 2.72]  
Total events  | 15  | 5  |  |  
Heterogeneity: Not applicable  
Test for overall effect: $Z = 0.75$ ($P = 0.45$)

Total (95% CI)  | 1394  | 474  | 100.0%  | 1.54 [1.27, 1.87]  
Total events  | 355  | 105  |  |  
Heterogeneity: $\chi^2 = 1.70$, df = 3 ($P = 0.64$); $I^2 = 0\%$  
Test for overall effect: $Z = 4.40$ ($P < 0.0001$)  
Test for subgroup differences: $\chi^2 = 0.18$, df = 1 ($P = 0.67$); $I^2 = 0\%$

(B) Study or Subgroup  |  Experimental Events  |  Control Total Events  |  Total Weight  |  Risk Ratio M.H. Fixed, 95% CI
---|---|---|---|---
2.2.1 2 weeks treatment  |  |  |  |  
Otomo 2003  | 63  | 125  | 47  | 125  | 35.8%  | 1.34 [1.01, 1.78]  
Sharma 2011  | 18  | 25  | 10  | 25  | 7.6%  | 1.80 [1.05, 3.08]  
Subtotal (95% CI)  | 150  | 150  | 43.4%  | 1.42 [1.10, 1.83]  
Total events  | 81  | 57  |  |  
Heterogeneity: $\chi^2 = 0.90$, df = 1 ($P = 0.34$); $I^2 = 0\%$  
Test for overall effect: $Z = 2.73$ ($P = 0.006$)

2.2.2 1 week treatment  |  |  |  |  
Kaste 2013  | 15  | 25  | 5  | 11  | 5.3%  | 1.32 [0.64, 2.72]  
Miyaj 2015  | 259  | 1129  | 43  | 313  | 51.3%  | 1.67 [1.14, 2.25]  
Subtotal (95% CI)  | 1154  | 324  | 56.6%  | 1.64 [1.24, 2.16]  
Total events  | 274  | 48  |  |  
Heterogeneity: $\chi^2 = 0.36$, df = 1 ($P = 0.55$); $I^2 = 0\%$  
Test for overall effect: $Z = 3.46$ ($P = 0.0005$)  
Test for subgroup differences: $\chi^2 = 0.54$, df = 1 ($P = 0.46$); $I^2 = 0\%$

Total (95% CI)  | 1394  | 474  | 100.0%  | 1.54 [1.27, 1.87]  
Total events  | 355  | 105  |  |  
Heterogeneity: $\chi^2 = 1.70$, df = 3 ($P = 0.64$); $I^2 = 0\%$  
Test for overall effect: $Z = 4.40$ ($P < 0.0001$)  
Test for subgroup differences: $\chi^2 = 0.54$, df = 1 ($P = 0.46$); $I^2 = 0\%$

(C) Study or Subgroup  |  Experimental Events  |  Control Total Events  |  Total Weight  |  Risk Ratio M.H. Fixed, 95% CI
---|---|---|---|---
2.3.1 Mean age $\geq 60$  |  |  |  |  
Kaste 2013  | 15  | 25  | 5  | 11  | 5.3%  | 1.32 [0.64, 2.72]  
Miyaj 2015  | 259  | 1129  | 43  | 313  | 51.3%  | 1.67 [1.14, 2.25]  
Otomo 2003  | 63  | 125  | 47  | 125  | 35.8%  | 1.34 [1.01, 1.78]  
Subtotal (95% CI)  | 1279  | 449  | 92.4%  | 1.52 [1.24, 1.87]  
Total events  | 337  | 95  |  |  
Heterogeneity: $\chi^2 = 1.29$, df = 2 ($P = 0.53$); $I^2 = 0\%$  
Test for overall effect: $Z = 4.01$ ($P < 0.0001$)

2.3.2 Mean age <60  |  |  |  |  
Sharma 2011  | 18  | 25  | 10  | 25  | 7.6%  | 1.80 [1.05, 3.08]  
Subtotal (95% CI)  | 25  | 25  | 7.6%  | 1.80 [1.05, 3.08]  
Total events  | 18  | 10  |  |  
Heterogeneity: Not applicable  
Test for overall effect: $Z = 2.14$ ($P = 0.03$)

Total (95% CI)  | 1394  | 474  | 100.0%  | 1.54 [1.27, 1.87]  
Total events  | 355  | 105  |  |  
Heterogeneity: $\chi^2 = 1.70$, df = 3 ($P = 0.64$); $I^2 = 0\%$  
Test for overall effect: $Z = 4.40$ ($P < 0.0001$)  
Test for subgroup differences: $\chi^2 = 0.32$, df = 1 ($P = 0.57$); $I^2 = 0\%$
Cl. $1.10-1.83$, $I^2 = 0$%; $P < 0.01$), and the pooled RR for patients treated with edaravone for 1 week was $1.64$ (95% CI, $1.24-2.16$, $I^2 = 0$%; $P < 0.01$) (Figure 5B). The third subgroup analysis was based on the mean age of patients. Three RCTs were conducted in patients with mean age equal to or over 60 years (RR = $1.52$, 95% CI, $1.24-1.87$, $I^2 = 0$%; $P < 0.01$), and one study was conducted in patients with mean age less than 60 (RR = $1.80$, 95% CI, $1.05-3.08$; $P = 0.03$) (Figure 5C). There was moderate evidence supporting the use of edaravone associated with an improvement of neurological impairment based on the European patients. However, the result was limited by the study size (20 events in 36 patients).

Additionally, as presented in Figure 6, three RCTs, with a total of 291 patients, including 143 patients in the observation group, evaluated the prognosis through NIHSS scores. The results showed that the $I^2$ value and $P$ value for evaluation of any treatment-related adverse events were 0 and 0.64, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 7A, there was no significant difference in the incidence of adverse reactions between two groups (RR = $0.83$, 95% CI: $0.51-1.34$, $P = 0.43$). Figure S1 shows that there was no evidence of publication bias for assessment of the incidence of adverse events.

Furthermore, the synthesis of data resulted in no significant differences between two groups in terms of occurrence of nausea (RR: $1.31$, 95% CI: $0.33-5.29$, $P = 0.7$; Figure 7B), skin rash (RR: $1.05$, 95% CI: $0.33-3.36$, $P = 0.93$; Figure 7C) and abnormal liver function (RR: $0.65$, 95% CI: $0.22-1.91$, $P = 0.43$; Figure 7D). Most reported treatment-related adverse events were of mild or moderate severity. Only two severe treatment-related adverse events were reported.18 In fact, this was a severe treatment-related adverse event (gout flare) reported twice in the same patient.

### 3.2.3 Adverse events

Four RCTs including 466 patients reported the incidence of adverse events during the treatment. In the control group, any treatment-related adverse events were found in 29 (12.1%) patients among 226 participants. Regarding the edaravone group, various adverse effects were observed in 28 (12.4%) patients among 240 participants.

The results showed that the $I^2$ value and $P$ value for evaluation of any treatment-related adverse events were 0 and 0.64, respectively, indicating no heterogeneity. Hence, the fixed-effects model was applied for meta-analysis. As presented in Figure 7A, there was no significant difference in the incidence of adverse reactions between two groups (RR = $0.83$, 95% CI: $0.51-1.34$, $P = 0.43$). Figure S1 shows that there was no evidence of publication bias for assessment of the incidence of adverse events.

Furthermore, the synthesis of data resulted in no significant differences between two groups in terms of occurrence of nausea (RR: $1.31$, 95% CI: $0.33-5.29$, $P = 0.7$; Figure 7B), skin rash (RR: $1.05$, 95% CI: $0.33-3.36$, $P = 0.93$; Figure 7C) and abnormal liver function (RR: $0.65$, 95% CI: $0.22-1.91$, $P = 0.43$; Figure 7D). Most reported treatment-related adverse events were of mild or moderate severity. Only two severe treatment-related adverse events were reported.18 In fact, this was a severe treatment-related adverse event (gout flare) reported twice in the same patient.

### 4 DISCUSSION

Along with the rapidly increasing ageing population and the constant rise of cardiovascular diseases, the incidence rate of acute ischaemic stroke has continued to rise year by year, posing a significant health burden.25 The progress of the acute ischaemic stroke would trigger local blood flow disorder, tissue ischaemia, hypoxia, and eventually, nerve cell necrosis. At this time, patients tend to present with various clinical symptoms such as hemiplegia and aphasia, indicating clinically gradual deterioration.26 Penumbra was proposed for the first time on the basis of a research conducted by Abstrup.27 In the early stage of ischaemia, cells in the ischaemic penumbra region...
will incur irreversible damage if blood flow cannot be recovered in time. Hence, saving the ischaemic penumbra plays a vital role in the management of AIS.

It is acknowledged that the culprits of ischaemic cerebrovascular injury are free radicals, which are mainly produced by the peroxidation of unsaturated fat in phospholipids within the cell membrane, damaging the cell membrane and thus facilitating secondary brain tissue damage. Edaravone is an antioxidant that has been produced in Japan since 2001 in the management of neurological and functional disorders as consequences of the acute ischaemic stroke. Theoretically, this antioxidant would scavenge free radical post-ischaemic events by alleviating the damage to neurons caused by oxidative stresses.

In this meta-analysis of randomized controlled trials, we determined the efficacy and safety of edaravone in the treatment of AIS patients. As expounded in our results, seven randomized controlled trials studies with 2069 patients were included. The pooled RR for improvement of neurological impairment at the three-month follow-up was 1.54 (95% CI, 1.27-1.87, $I^2 = 0$, $P < 0.01$) in four RCTs. For the incidence of mortality, the pooled RR for studies that evaluated edaravone at the three-month follow-up was 0.55 (95% CI, 0.45-0.7, $I^2 = 0$, $P < 0.01$). For the incidence of any treatment-related adverse events during therapy any treatment-related adverse events (A), nausea (B), skin rash (C), abnormal liver function (D). 150 × 150 mm (300 × 300 DPI)
adverse events, the pooled RR for studies that evaluated edaravone during treatment was 0.83 (95% CI, 0.51-1.34, $I^2 = 0$, $P = 0.43$). We confirmed that edaravone improved the neurological impairment at three-month follow-up. A significant reduction of mortality was observed in the edaravone group at three-month follow-up. Additionally, there was no significant difference in the incidence of adverse reactions between the edaravone group and the control group. This current investigation indicates that edaravone is effective and safe in the management of AIS.

We acknowledge that there are still some limitations in the current investigation. First, only subjects from Asia and European countries were included in this investigation. We call for more reliable RCTs on the AIS patients from other continents. Second, due to the incomplete data, our meta-analysis did not focus on the specific ischaemic stroke subtype. More well-designed studies are required to explore the efficacy and safety of this antioxidant in different ischaemic stroke subtypes. Third, we acknowledge that our research included only one large RCT, which itself had reporting bias and contributed the majority of the data. Hence, we call for more well-designed RCTs with larger sample sizes performed in Western countries. Last, only articles in English were included in this current research, which may contribute to information bias.

5 | WHAT IS NEW AND CONCLUSION

Collectively, our current study confirms that edaravone can improve neurological impairment with a definite effect at three-month follow-up, regardless of the mean age and course of treatment. Edaravone is also safe in the management of AIS. It is worthy of promotion in clinical treatment of AIS in Asian countries. More well-designed RCTs with larger sample sizes are needed to determine the benefits of edaravone in patients from Western countries.

ACKNOWLEDGEMENTS

The authors would like to thank all the staff at the Library in the First Affiliated Hospital of Shantou University Medical College for their great support and conscientious work during the literature search of this study.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

CC and ML contributed equally to this study. CC and ML planned the study. CC, SC and ML screened the literature and collected data. CC, SC and ML conducted the study quality assessment. ML, LL and YC performed the meta-analysis and wrote the manuscript. LH conducted the study supervision and critical revision.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the author upon request.

REFERENCES

1. Wang Y, Han S, Qin H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of the management of high-risk population. Stroke Vasc Neurol. 2020;5:270-278.
2. Liu L, Chen W, Zhou H, et al. Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders: executive summary and 2019 update of clinical management of ischaemic cerebrovascular diseases. Stroke Vasc Neurol. 2020;5:159-176.
3. Felberg R, Burgin W, Grotta J. Neuroprotection and the ischemic cascade. CNS Spectr. 2000;5:52-58.
4. Shakour Z, Issa H, Ismail H, et al. Drug repurposing: promises of edaravone target drug in traumatic brain injury. Curr Med Chem. 2020;27: https://doi.org/10.2174/09298673276662008122 21022
5. Abe K, Yuki S, Kogure K. Strong attenuation of ischemic and postischemic brain edema in rats by a novel free radical scavenger. Stroke. 1988;19:480-485.
6. Nishi H, Watanabe T, Sakurai H, Yuki S, Ishibashi A. Effect of MCI-186 on brain edema in rats. Stroke. 1989;20:1236-1240.
7. Oishi R, Itoh Y, Nishibori M, Watanabe T, Nishi H, Saeki K. Effect of MCI-186 on ischemia-induced changes in monoamine metabolism in rat brain. Stroke. 1989;20:1557-1564.
8. Watanabe T, Yuki S, Egawa M, Nishi H. Protective effects of MCI-186 on cerebral ischemia: possible involvement of free radical scavenging and antioxidant actions. J Pharmacol Exp Ther. 1994;268:1597-1604.
9. Yamamoto T, Yuki S, Watanabe T, Mitsuka M, Saito K, Kogure K. Delayed neuronal death prevented by inhibition of increased hydroxyl radical formation in a transient cerebral ischemia. Brain Res. 1997;762:240-242.
10. Yamamoto Y, Kuwashara T, Watanabe K, Watanabe K. Antioxidant activity of 3-methyl-1-phenyl-2-pyrazolin-5-one. Redox Rep. 1996;2:333-338.
11. Kimura K, Aoki J, Sakamoto Y, et al. Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients—a preliminary study. J Neurol Sci. 2012;313:132-136.
12. Kobayashi S, Fukuma S, Ikenoue T, Fukuhara S, Kobayashi S. Effect of edaravone on neurological symptoms in real-world patients with acute ischemic stroke. Stroke. 2019;50:1805-1811.
13. Yang J, Cui X, Li J, Zhang C, Zhang J, Liu M. Edaravone for acute stroke: Meta-analyses of data from randomized controlled trials. Dev Neurorehabil. 2015;18:330-335.
14. Abe M, Kaizu K, Matsumoto K. A case report of acute renal failure and fulminant hepatitis associated with edaravone administration in a cerebral infarction patient. Ther Apher Dial. 2007;11:235-240.
15. Shamsaeer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.
17. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.
18. Kaste M, Murayama S, Ford G, Dippel D, Walters M, Tatlisumak T. Safety, tolerability and pharmacokinetics of MCI-186 in patients with acute ischemic stroke: new formulation and dosing regimen. Cerebrovasc Dis. 2013;36:196-204.
19. Li X, Ma D, Sun G. Effects of edaravone on neurological function and tumor necrosis factor alpha and interleukin 8 levels in patients with cerebral infarction. Eur Neurol. 2020;83:73-79.
20. Miyaji Y, Yoshimura S, Sakai N, et al. Effect of edaravone on favorable outcome in patients with acute cerebral large vessel occlusion: subanalysis of RESCUE-Japan Registry. Neurol Med Chir. 2015;55:241-247.

21. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. Cerebrovasc Dis. 2003;15:222-229.

22. Sharma P, Sinha M, Shukla R, Garg R, Verma R, Singh M. A randomized controlled clinical trial to compare the safety and efficacy of edaravone in acute ischemic stroke. Ann Indian Acad Neurol. 2011;14:103-106.

23. Sun Z, Xu Q, Gao G, Zhao M, Sun C. Clinical observation in edaravone treatment for acute cerebral infarction. Nigerian J Clin Pract. 2019;22:1324-1327.

24. Zheng J, Chen X. Edaravone offers neuroprotection for acute diabetic stroke patients. Ir J Med Sci. 2016;185:819-824.

25. Bravata D, Ho S, Meehan T, Brass L, Concato J. Readmission and death after hospitalization for acute ischemic stroke: 5-year follow-up in the medicare population. Stroke. 2007;38:1899-1904.

26. Li Y, Wei Y, Cao Y, Lu X, Yao Y, Wang L. Severe cerebral edema induced by watershed shift after bypass in a patient with chronic steno-occlusive disease: a case report and short literature review. BMC Neurol. 2020;20:335.

27. Astrup J, Symon L, Branston N, Lassen N. Cortical evoked potential and extracellular K+ and H+ at critical levels of brain ischemia. Stroke. 1977;8:51-57.

28. Ran Y, Zhu M, Li S, et al. Related research and recent progress of ischemic penumbra. World Neurosurg. 2018;116:5-13.

29. Tomassoni D, Amenta F, Amantini C, et al. Brain activity of thioctic Acid enantiomers: in vitro and in vivo studies in an animal model of cerebrovascular injury. Int J Mol Sci. 2013;14:4580-4595.

30. Yamamoto Y. Plasma marker of tissue oxidative damage and edaravone as a scavenger drug against peroxyl radicals and peroxynitrite. J Clin Biochem Nutr. 2017;60:49-54.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Chen C, Li M, Lin L, Chen S, Chen Y, Hong L. Clinical effects and safety of edaravone in treatment of acute ischaemic stroke: A meta-analysis of randomized controlled trials. J Clin Pharm Ther. 2021;46:907–917. https://doi.org/10.1111/jcpt.13392