Edaravone for acute ischaemic stroke (Review)

Feng S, Yang Q, Liu M, Li W, Yuan W, Zhang S, Wu B, Li J

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[Intervention Review]

Edaravone for acute ischaemic stroke

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ABSTRACT

Background

Neuroprotection is a promising therapeutic strategy for the treatment of acute ischaemic stroke. Edaravone is a neuroprotective agent that has been widely used in China, and several studies have suggested that it may be beneficial in acute ischaemic stroke.

Objectives

To assess the efficacy and safety of edaravone for acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (November 2010) and the Chinese Stroke Trials Register (November 2010). In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4), MEDLINE (1950 to November 2010), EMBASE (1980 to November 2010), China National Knowledge Infrastructure (1979 to November 2010), Chinese Biomedical Database (1979 to November 2010), Chinese Evidence-Based Medicine Database (November 2010) and Chinese Science and Technology Journals Database (1980 to November 2010). In an attempt to identify further published, unpublished and ongoing trials we searched reference lists and clinical trials and research registers, and contacted a pharmaceutical company, researchers and study authors.

Selection criteria

We included randomised controlled trials comparing edaravone with placebo or no intervention in patients with acute ischaemic stroke.

Data collection and analysis

Two review authors selected trials for inclusion, assessed trial quality and independently extracted the data.

Main results

We included three trials, involving 496 participants, and defined four trials as waiting assessment. All three included trials were of edaravone plus another treatment compared with the other treatment alone. The dose of edaravone injections in the three trials was the same at 60 mg per day. The course of treatment in all three trials is 14 days. None of the included trials reported the pre-specified primary outcome of death or dependency defined using the modified Rankin scale during the follow-up period. The three trials evaluated the

effect of edaravone at different times and using different methods. All three trials reported adverse events; there were no differences between the treatment group and the control group. Overall, edaravone appeared to increase the proportion of participants with marked neurological improvement compared with the control group, and the difference was significant (risk ratio (RR) 1.99, 95% confidence interval (CI) 1.60 to 2.49).

Authors' conclusions

The risk of bias in the included trials was moderate and the sample was small. Hence, although the data in this review show an effective treatment trend of edaravone for acute ischaemic stroke, further large, high-quality trials are required to confirm this trend.

PLAIN LANGUAGE SUMMARY

Edaravone for acute ischaemic stroke

Most strokes take place when a blood clot blocks a blood vessel leading to the brain. Without a proper blood supply, the brain quickly suffers damage, which can be permanent. The damage from a stroke can cause arm or leg weakness, or difficulties with language or vision. Data from some experimental and human studies have suggested that edaravone, a neuroprotective agent, may be beneficial for people with acute ischaemic stroke. It has been widely used in China to treat stroke. To obtain a reliable assessment of the effects of edaravone in acute ischaemic stroke, we reviewed data from three studies involving 496 participants. The quality of the trials was moderate. It would appear that edaravone is an effective treatment for acute ischaemic stroke. However, more high-quality and bigger sample trials are needed to confirm this result.

BACKGROUND

Stroke is the second commonest cause of death and the leading cause of disability worldwide (Liu 2007). Approximately 87% of all strokes are ischaemic, that is due to a blockage of an artery in the brain (AHA 2007). Even though enormous efforts have focused on the development of drugs to limit brain damage caused by acute ischaemic stroke, there is as yet no routine, effective, generally accepted, specific treatment for acute ischaemic stroke except for aspirin (Sandercock 2008) and thrombolysis with tissue plasminogen activator (within 4.5 hours of stroke onset) (Wardlaw 2003). Therefore, it is necessary to test other promising strategies such as neuroprotective agents.

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a novel, potent, free radical scavenger. It was first reported to have a beneficial effect in animal models of stroke in the late 1980s (Abe 1988; Nishi 1989; Oishi 1989). In June 2001, it was approved by the Japanese regulatory authorities as the first free radical scavenger for clinical use in the management of acute ischaemic stroke (Green 2005). Now it is widely used in China.

Numerous experimental studies have shown that edaravone has neuroprotective properties due to its antioxidant effects - the reported mechanisms are as follows: (1) quenching hydroxyl radical (OH) and inhibiting OH-dependent and OH-independent lipid peroxidation (Watanabe 1994; Yamamoto 1997); (2) exerting a wide range of inhibitory effects on both water-soluble and lipid-soluble peroxyl radical-induced peroxidation systems, which are similar to the combined effects of vitamins C and E (Yamamoto 1996); and (3) inhibiting both non-enzymatic lipid peroxidation and lip-oxygenase pathways and having potent antioxidant effects against ischaemia or reperfusion-induced vascular endothelial cell injury, delayed neuronal death, brain oedema and concomitant neurological deficits (Yamamoto 1996).

Many clinical studies have been conducted to assess the efficacy of edaravone for ischaemic stroke. A multicentre, randomised, placebo-controlled, double-blind trial showed that edaravone significantly improves functional outcome in patients with acute ischaemic stroke (EAIS Group 2003). However, a systematic review of eight trials of edaravone for acute ischaemic stroke, published in 2006 (Yang 2006b), and another recent review (Lapchak 2010) found no conclusive evidence of efficacy of edaravone and further trials are needed. Since 2006 more trials have been conducted in China. There have been reports of fatal adverse events (due to acute kidney failure) associated with the use of edaravone (Green 2005). Therefore, before edaravone is recommended for routine use in patients with acute ischaemic stroke, its efficacy and safety should be rigorously assessed through a Cochrane Review.

OBJECTIVES

To assess the efficacy and safety of edaravone for acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials comparing edaravone with placebo or no intervention in patients with acute ischaemic stroke. We excluded confounded trials in which the treatment or control group received another active therapy (for example, edaravone agents versus another drug).

Types of participants

Trials which included participants of any age or sex with acute ischaemic stroke (within three days of onset) were eligible. The clinical definition of ischaemic stroke was that of the World Health Organization (Hatano 1976) with computerised tomography (CT) or magnetic resonance imaging (MRI) to exclude haemorrhagic stroke.

Types of interventions

We included trials that compared edaravone with placebo or no intervention. We included trials regardless of dose or duration. We allowed additional interventions if received by all groups in the trial.

Types of outcome measures

Primary outcome measure

1. Mortality or disability at the end of follow-up (at least three months). We defined disability as dependent on others in activities of daily living (e.g. Barthel Index score of 60 or less, or modified Rankin Scale graded 3 to 5 (Sulter 1999), or the trialist's own definition).

Secondary outcome measures

1. Death from any cause during the first two weeks of treatment, and during the whole follow-up period
2. Kidney failure.
3. Adverse events: nausea, vomiting, allergic reaction, tachycardia, haemorrhagic transformation of the infarct caused by edaravone and some unexplained organ abnormalities (for example, renal, hepatic, haematological, cardiac and respiratory). The number of patients developing at least one adverse event listed was evaluated.
4. The proportion of patients with marked neurological improvement after treatment. The measures could focus on specific impairment (for example motor deficit or cognitive impairment) or global neurological deficit (for example the National Institute of Health Stroke Scale, Canadian Neurological Scale, European Stroke Scale or the Scandinavian Stroke Scale, which involve motor, sensory and other impaired neurological function).
5. Quality of life if assessed by the included trials.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register (last searched November 2010) and the Chinese Stroke Trials Register (last searched November 2010). In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4), MEDLINE (1950 to November 2010) (Appendix 1) and EMBASE (1980 to November 2010) (Appendix 2). We developed the MEDLINE and EMBASE search strategies in consultation with the Cochrane Stroke Group Trials Search Co-ordinator. We also searched the following Chinese databases:

- China National Knowledge Infrastructure (CNKI) (1979 to November 2010);
- Chinese Biomedical Database (CBM) (1979 to November 2010);
- Chinese Evidence-Based Medicine Database (last searched November 2010); and
- Chinese Science and Technology Journals Database (VIP) (1980 to November 2010).

In an effort to identify further published, unpublished and ongoing studies:

- we searched the following relevant ongoing trials registers:
  - Stroke Trials Directory (http://www.strokecenter.org/trials/);
  - National Institute of Health Clinical Trials Database (http://www.clinicaltrials.gov/);
- we contacted the pharmaceutical company (Simcere Pharmaceutical Group) manufacturing edaravone;
- we contacted colleagues and researchers and attempted to contact study authors to obtain further data; and
- we searched reference lists of relevant trials.

Data collection and analysis

Study selection

Two review authors (SF, QY) scrutinised the titles and abstracts of all articles identified in the electronic databases and excluded those that were clearly not relevant. We obtained the full text of all the remaining articles and from these we selected the studies for inclusion. We resolved disagreements through discussion or with a third review author (ML) if necessary.

Two review authors (SF, QY) independently extracted data on the methods, patients, interventions, outcomes and results, and recorded the information on a data extraction form. The key information extracted was as follows.

1. General information: published/unpublished, title, authors, reference/source, contact address, country, language of publication, year of publication, duplicate publications, sponsor, setting.
2. Trial characteristics: design, duration of follow-up, method of randomisation, allocation concealment, blinding (patients, people administering treatment, people assessing outcome).
3. Interventions: intervention (dose, route, frequency, duration), controlled intervention (dose, route, frequency, duration), co-medication(s) (dose, route, frequency, duration).
4. Patients: inclusion/exclusion criteria, diagnostic criteria, total number and number in each groups, age, baseline characteristics, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals (reasons/ description), subgroups.
5. Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes.

The same two review authors independently undertook the selection of eligible trials and the evaluation of the methodological quality of these trials; these review authors were unblinded with regard to the names of the authors, investigators, institutions and results. We discussed discrepancies and disagreements until we reached a consensus. If necessary, a third review author (ML) participated to resolve disagreements. We provided the reason for each excluded trial. When patients were excluded or lost to follow-up after randomisation, or if any of the above data were unavailable from the publications, we sought further information by contacting the study authors. If such information remained unavailable, all the review authors decided whether or not to include the trial in the review.

Quality assessment

At least two review authors independently assessed methodological quality using the following criteria that are described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We resolved disagreements through discussion or with a third review author (ML) if necessary.

Generation of the allocation sequence

- Adequate: by table of random numbers, computer-generated random numbers, coin tossing, shuffling or similar.
- Unclear: the trial was described as random allocation, but the generation of the allocation sequence was not described.
- Inadequate: a quasi-randomised study was defined as involving dates, names or admittance numbers to allocate patients (these were excluded from the review).

Allocation concealment

- Adequate: concealed up to the point of treatment by central randomisation, opaque sealed envelopes or similar.
- Unclear: the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate: the allocation sequence was known to the investigators who assigned participants, such as open table of random numbers or quasi-randomised or similar. We excluded quasi-randomised studies from the review.

Blinding

- Adequate: using identical placebo or similar.
- Unclear: the trial was described as blinded, but the method of blinding was not described.
- Not performed: different type of intervention between groups, for example, oral administration versus injection or similar.

Follow-up

- Adequate: the result is known although the participant is a drop-out.
- Unclear: the report gave the impression that there were no drop-outs or withdrawals, but this was not specifically stated.
- Inadequate: the number and reasons for drop-outs and withdrawals were not described.

In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008), methodological quality was described as:

A: low risk of bias - all quality criteria met;

B: moderate risk of bias - one or more of the quality criteria only partly met;

C: high risk of bias - one or more criteria not met.

Furthermore, we also recorded intention-to-treat analysis and sample size calculations.

Data extraction

Two review authors (SF, QY) independently extracted the data from the included randomised trials. If necessary, we contacted study authors by e-mail or telephone to obtain missing data or

to clarify methodology. We extracted the following data using a standardised form.

- Trial characteristics: study ID, source.
- Methodology: method of randomisation, allocation concealment, blinding and number of patients with follow-up.
- Patient characteristics: number of patients randomised to each arm, mean or median age, ratio of males and length of follow-up.
- Intervention characteristics: type and dose in each group, duration of therapy and additional interventions.
- Outcomes: all outcomes were extracted from each trial.

Data synthesis

We performed statistical analysis using the Review Manager software, RevMan 5.1 (RevMan 2011). We performed all analyses in accordance with the intention-to-treat method, which includes all randomised patients regardless of loss of follow-up. We explored statistical heterogeneity among results of different studies using the Chi^2 test with significance set at $P < 0.1$. We measured the percentage of variation between trial results that is due to heterogeneity rather than chance using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity (Higgins 2003). We expressed dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI), and mean difference (MD) or standardised mean difference (SMD) and 95% CI for continuous outcomes. We used a fixed-effect model to combine individual results if there was no significant heterogeneity among the included trials; otherwise, we used the random-effects model.

If possible, we performed sensitivity analyses with low bias-risk trials and subgroup analyses as follows:

1. the timing of treatment after stroke onset (for example, less than 12 hours, 12 to 48 hours, 48 hours to three days);
2. dose (low and high, based on data);
3. length of treatment.

We tested significant differences between two or more subgroups using the Chi^2 test, in which P value for Qint (Qint = Qall - (Q1 + ¡ + Qm)) on m-1 degrees of freedom was computed using Excel software. Qall is the Chi^2 heterogeneity statistic for all included trials, Q1 to Qm are Chi^2 heterogeneity statistics for each subgroup.

We planned to use funnel plot asymmetry to assess the existence of publication bias if more than nine trials were included (Egger 1997).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

We identified 1788 references through electronic searches and handsearches. Of these, we excluded 1764 irrelevant references. We identified 24 potentially eligible trials, of which three were included (Otomo 2003; Zhang 2007; Zhou 2007). The summary details of these trials are given in the Characteristics of included studies table. We excluded 15 trials (Du 2006; Guo 2008; He 2007; Hu 2008; Long 2008; Shan 2009; Wang 2005a; Wang 2005b; Wang 2006; Wang 2007; Xu 2008a; Xu 2008b; Yang 2006a; Yu 2007; Zhang 2006) because they were not randomised trials. Two trials are currently ongoing (Goel 2009; Mitsubishi Tanabe 2010). Four trials (Di 2004; Gu 2005; Minematsu 2009; Zhou 2007a) are defined as awaiting assessment because the authors of three of them (Di 2004; Gu 2005; Zhou 2007a) could not be contacted by telephone or email, so we were unable to clarify whether the trials were randomised. The fourth trial (Minematsu 2009) is awaiting assessment because we were unable to get enough information to include or exclude it.

One of the three trials was conducted in Japan, two were conducted in China. Two trials (Otomo 2003; Zhou 2007) reported the average age of the participants which ranged from 57 to 74.3 years. The other trial (Zhang 2007) did not report the average age or the age range.Two trials (Otomo 2003; Zhou 2007) included more males than females. The other trial (Zhang 2007) did not provide these data. All three trials had distinct inclusion and exclusion criteria.

All three trials were of edaravone plus another treatment compared with the other treatment alone. The dose of edaravone injections in the three trials was the same at 60 mg per day.

The course of treatment in all three trials was 14 days. One trial (Otomo 2003) reported that the average timing range of the start of treatment after stroke onset was from 14.7 to 55.9 hours. One trial (Zhang 2007) reported the time at less than 72 hours, the other trial (Zhou 2007) stated the time was less than 24 hours. Two trials (Zhang 2007; Zhou 2007) reported the severity of the strokes using the European Stroke Scale: in Zhang 2007 the range is 41 to 67 (edaravone group) and 44 to 72 (placebo group), in Zhou 2007 the range is 49 to 78.2 (edaravone group) and 49.4 to 75 (placebo group). Otomo 2003 reported the grade of neurological deficits as defined by the study authors. All the trials reported that there was no difference between two groups.

Only Otomo 2003 reported death: four in the edaravone group. The reason was exacerbation of brain infarction, sudden cardiac arrest, pneumonia and suicide due to the mental depression in one patient each. No kidney failure was reported in any of the trials.

All the included trials evaluated the effect of edaravone at different times and using different methods. Otomo 2003 evaluated the effect of edaravone at three, six and 12 months after onset with improvement of neurological deficit according to the modified Rankin Scale. The two Chinese trials evaluated the effects at

different times in different methods: Zhang 2007 evaluated the effect of edaravone at seven, 14 and 28 days on the proportion of participants with improvement of neurological deficit according to European Stroke Scale and Activities of Daily Living Scale; Zhou 2007 evaluated the effect of edaravone at the end of the treatment (14 days) on the proportion of participants with improvement of neurological deficit according to the European Stroke Scale.

All the trials reported adverse events. In Otomo 2003 adverse reactions were observed in nine patients (7%) in the edaravone group and in 14 patients (11%) in the placebo group. Such reactions in the edaravone group consisted of a skin rash in four patients, abnormal liver function in three patients, itching and nausea in one patient, and fever and abnormal liver function in one patient, but recovery was achieved during or after the treatment. In Zhang 2007 adverse reactions were observed in 4% of patients in the edaravone group and in 6.9% of patients in the placebo group. Such reactions in the edaravone group consisted of nausea, vomiting, diarrhoea, skin rash, headache, abnormal liver function, leukopenia and cardiopalmus, but recovery was achieved during or after the treatment. In Zhou 2007 no patient had an adverse event in the edaravone group. Only one trial (Zhang 2007) evaluated quality of life using the Activities of Daily Living scale.

Risk of bias in included studies

Otomo 2003 reported randomly allocating patients but the method of randomisation was not described. Zhang 2007 reported the use of a random digit table to divide the edaravone group and control groups. Zhou 2007 reported the use of computer-based randomisation to divide the edaravone group and control groups. None of the three trials reported the method of allocation concealment and were graded as having unclear allocation concealment. All the trials used placebo to achieve blinding.

The follow-up period in the three trials was different. Two trials (Otomo 2003; Zhou 2007) reported drop-outs: one trial (Otomo 2003) used intention-to-treat analysis, the other (Zhou 2007) used worst-case scenario analysis. All the studies stated that the baseline characteristics of the participants were similar between the two comparison groups.

Effects of interventions

Death or dependency at the end of scheduled follow-up

None of the trialists reported death and dependency simultaneously at the end of long-term follow-up.

Death from all causes within the first two weeks of treatment, and during the whole follow-up period

Data were available from one trial (Otomo 2003) with 250 participants. Edaravone therapy was not associated with a significant reduction in death during the whole follow-up period (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.22 to 2.91).

The proportion of participants with marked neurological improvement after treatment

The outcomes measured after treatment were assessed according to European Stroke Scale in two trials. Meta-analysis of the two trials that used a dichotomous outcome variable showed that a significantly higher proportion of participants treated with edaravone had an improvement of their neurological deficit at the end of treatment compared with the control participants (RR 1.93, 95% CI 1.54 to 2.43). One trial measured neurological deficit according to the modified Rankin Scale. There was a significantly higher proportion of participants with marked neurological improvement in the edaravone group (RR 2.25, 95% CI 1.19 to 4.24). Overall, edaravone appeared to increase the proportion of participants with marked neurological improvement compared with the control group, and the difference was significant (RR 1.99, 95% CI 1.60 to 2.49).

DISCUSSION

We included three trials (Otomo 2003; Zhang 2007; Zhou 2007), which involved 496 participants. The trials we included in this review are different to those included in the previously published review on edaravone for acute ischaemic stroke (Yang 2006b).

We excluded six trials that were included in the previously published review because they were not randomised trials, and defined two trials included in the previous review as awaiting assessment because we could not confirm that they were randomised trials. We also found another two meta-analyses (Li 2009; Qin 2010) which only included Chinese trials and were not completed according to Cochrane methodology. The meta-analysis of the three included trials showed that edaravone may improve neurological impairment after acute ischaemic stroke, but this result should be interpreted with caution because of the small number of participants and the moderate quality of the trials.

None of the included trials reported the pre-specified primary outcome of death or dependency defined using the modified Rankin Scale during the follow-up period. All the trials were at the level of neurological deficit. Otomo 2003 followed up the participants until 12 months after onset, Zhang 2007 followed up the participants until 28 days after the beginning of the treatment, and Zhou 2007 followed up the participants until 14 days after the beginning of the treatment.

Only Otomo 2003 reported death. It is possible that only mild strokes were included in other two trials, or that the authors attempted to emphasise the positive role of edaravone by not reporting deaths, or that there were no deaths during the short-term follow-up period. Lack of death reporting is a major methodological concern. Reports of randomised trials should conform to the requirements of the CONSORT statement (www.consort-statement.org), which includes reporting all clinically relevant outcomes, including deaths.

There were some methodological defects in the design and performance of the included trials: Otomo 2003 reported 'randomly allocating' participants but did not report the method of randomisation; Zhou 2007 reported that the method of randomisation was computer-based; and Zhang 2007divided the groups using a random number table (we obtained this information from the study authors).

None of the three trials reported the method of allocation concealment and were graded as 'unclear' for allocation concealment. All of the trials stated they used placebo to achieve blinding. Otomo 2003 reported that they used intention-to-treat analysis, Zhou 2007 reported that they used worst-case scenario analysis, and Zhang 2007 did not state whether or not they used intention-to-treat analysis. Two trials (Otomo 2003; Zhou 2007) reported the number of drop-outs; Zhang 2007 did not provide these data. These trials were only of moderate quality, which may have led to selection or performance bias resulting in the effect of edaravone being exaggerated. Moreover, an unusually high proportion of trials with positive results are published in the Chinese literature (Vickers 1998), and two of the three included trials were conducted in China and published in Chinese.

All three trials reported adverse events - there was no difference between the treatment group and the control group. However, the sample size was small and two trials did not follow up the participants for long enough, so these trials may not reflect the long-term effect of the intervention.

The efficacy and safety of edaravone for acute ischaemic stroke was influenced to some extent by the moderate quality of the included trials. Further well-designed randomised controlled trials with widely-applied outcome measures are therefore required.

AUTHORS' CONCLUSIONS

Implications for practice

The risk of bias in all the included trials was moderate and the sample was small. Hence, although the data in this review show an effective treatment trend of edaravone for acute ischaemic stroke, larger samples and higher quality trials are needed to confirm this trend.

Implications for research

This review suggests that edaravone may improve neurological impairment in the treatment of acute ischaemic stroke. However, since the observed effects may have been due to bias rather than a true biological effect, further randomised controlled studies are justified to assess the efficacy and safety of edaravone for patients with acute ischaemic stroke. The design and performance of future research should take the following into consideration.

1. Appropriate methods of randomisation to generate the allocation sequence.

2. Large sample size.

3. Adequate allocation concealment.

4. Blinding of investigator, participants and outcome assessors.

5. The use of standard validated outcome measures measured some months after randomisation.

6. Complete follow-up of all randomised participants.

7. Reporting of all deaths and adverse events, critically assessed by standardised monitoring or an effective self report system.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Otomo 2003

Methods	RCT: random allocation was reported but the method of randomisation and concealment not reported ITT analysis: the data were subjected to ITT analysis Losses to follow-up: none
Participants	Inclusion criteria: (1) inpatients within 72 hours after the onset of ischaemic stroke including patients with strokes that were both thrombotic and embolic in nature, (2) patients with a level of consciousness between 0 (alert) and 30 (able to be aroused with mechanical or verbal stimuli) Exclusion criteria: not reported Country: Japan 252 participants (125 treatment, 127 control) Comparability: age, sex, time to treatment after stroke onset, level of consciousness before treatment, aggregate score for neurological deficits before treatment, associated disease, CT or MRI findings before treatment The timing of the start of the treatment after stroke onset not reported
Interventions	Treatment: edaravone 30 mg twice daily for 14 days Control: placebo twice daily for 14 days
Outcomes	Comparisons of modified Rankin Scale were undertaken by Wilcoxon's rank sum test, which has the criterion for significance set at 5% (two-tailed)
Notes	Follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation was reported but the method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	Random method of concealment was not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding reported but the method of blinding was not described

Zhang 2007

Methods	RCT: random allocation was reported and the method of randomisation was generated by computer. The concealment was not reported ITT analysis: not reported Losses to follow-up: none
Participants	Inclusion criteria: start within 72 hours, carotid system cerebral infarction,18 to 70 years old, awareness score of ESS more than 6 points, ESS score less than 80 points, first ever stroke or recurrent stroke patients in whom paralysis of limbs does not affect the neurological function evaluation, signed informed consent form, inpatients and clinical diagnosis of acute ischaemic stroke (CT scan proven) Exclusion criteria: allergies; taking other related brain protective agents; had taken part in other clinical trials within 3 months; liver, kidney or heart dysfunction; illiteracy; dementia; mental illness; serious diseases of other systems; pregnancy, intended pregnancy and lactating patients; patients with poor compliance Country: China 202 participants (100 treatment, 102 control) Comparability: age, sex, weight, time to treatment after stroke onset, combination therapy The timing of the start of treatment after stroke onset not reported
Interventions	Treatment: edaravone 30 mg twice daily for 14 days Control: saline twice daily for 14 days Both groups: same basic drug therapy
Outcomes	Number of participants with neurological improvement (ESS and ADL increasing rate > 16%) at 7, 14 days and 28 days
Notes	Follow-up: 28 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation was reported and the method of randomisation is generated by computer
Allocation concealment (selection bias)	Unclear risk	Random method reported but the method of concealment was not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding reported but the method of blinding was not described

Zhou 2007

Methods	RCT: random allocation was reported and the method of randomisation and concealment were reported ITT analysis: the data were subjected to worst-case scenario analysis Losses to follow-up: none
Participants	Inclusion criteria: first ever mild or moderate internal carotid arteries complete thrombotic cerebral infarction, patients with stroke history but complete recovery, 18 to 75 years old, start within 48 hours, awareness score of the ESS is more than 6 points, ESS score less than 80 points, clinical diagnosis of acute ischaemic stroke (CT scan proven) and a signed informed consent form Exclusion criteria: complicated with pneumonia, brain tumour, brain trauma and other brain lesions; cardiac insufficiency; chronic liver disease - alanine transaminase increased more than 2 times the normal value; renal dysfunction - serum creatinine increased more than 133 mmol/l; after treatment blood pressure less than 90/60 mmHg or higher than 200/110 mmHg; recent haemorrhagic disease; patients with severe mental illness; allergies; pregnant or breast-feeding women Country: China 44 participants (22 treatment, 22 control) Comparability: age, sex, pre-treatment severity of disease, neurological deficit score, BI difference The timing of the start of treatment after stroke onset not reported
Interventions	Treatment: edaravone 30 mg twice daily for 14 days Control: placebo twice daily for 14 days Both groups: same basic drug therapy
Outcomes	ESS score and BI score between pre-treatment and after 14 of days treatment
Notes	Follow-up: 14 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation was reported and method of randomisation is generated by computer
Allocation concealment (selection bias)	Unclear risk	Random method reported and the method of concealment was not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding reported and the method of blinding was described

ADL: activities of daily living
BI: Barthel Index
CT: computerised tomography

ESS: European Stroke Scale
ITT: intention-to-treat
MRI: magnetic resonance imaging
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Du 2006	Not a RCT
Guo 2008	Not a RCT
He 2007	Not a RCT
Hu 2008	Not a RCT
Long 2008	Not a RCT
Shan 2009	Not a RCT
Wang 2005a	Not a RCT
Wang 2005b	Not a RCT
Wang 2006	Not a RCT
Wang 2007	Not a RCT
Xu 2008a	Not a RCT
Xu 2008b	Not a RCT
Yang 2006a	Not a RCT
Yu 2007	Not a RCT
Zhang 2006	Not a RCT

RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Di 2004

Methods	RCT: random allocation was reported but method of randomisation and concealment was not reported Blinding: double-blind ITT analysis: not reported Losses to follow-up: none
Participants	Inclusion criteria: carotid system cerebral infarction confirmed by CT or MRI to exclude cerebral haemorrhage, first ever stroke or recurrent stroke patients in whom paralysis of limbs does not affect neurological function evaluation, 40 to 80 years old, no limitation on sex, awareness score of the ESS more than 6 points, ESS score less than 80 points, within the first 48 hours from onset, no systemic complications, signed informed consent form Exclusion criteria: patients associated with severe heart and lung liver and kidney dysfunction, other organic brain disease, serious mental illness, dementia patients, and allergy patients Country: China 70 participants (35 treatment, 35 control) Comparability: age, sex, course, ADL score, ESS score, associated diseases, infarct site The timing of the start of the treatment after stroke onset not reported
Interventions	Treatment: edaravone 30 mg twice daily for 14 days plus basic treatment for 21 days Control: placebo twice daily for 14 days plus basic treatment for 21 days
Outcomes	Efficacy was determined by increasing fraction of ESS and ADL score Calculated as follows: increasing fraction = (points after treatment - treatment the former points) / (100 - points before treatment) *100%
Notes	Follow-up: 21 days

Gu 2005

Methods	RCT: random allocation was reported but method of randomisation and concealment was not reported Blinding: double-blind ITT analysis: not reported Losses to follow-up: 7
Participants	Inclusion criteria: carotid system cerebral infarction confirmed by CT to exclude cerebral haemorrhage, first ever stroke or recurrent stroke patients in whom paralysis of limbs does not affect neurological function evaluation,18 to 80 years old, no limitation on sex, awareness score of the ESS more than 6 points, ESS score less than 80 points, within the first 48 hours from onset, no systemic complications, signed informed consent form Exclusion criteria: unclear Country: China 213 participants (109 treatment, 104 control) Comparability: age, sex, course, ADL score, ESS score, associated diseases, body weight, past medical history The timing of the start of the treatment after stroke onset not reported
Interventions	Treatment: edaravone 30 mg twice daily for 14 days plus basic treatment for 21 days Control: placebo twice daily for 14 days plus basic treatment for 21days

Gu 2005 (*Continued*)

Outcomes	Efficacy was determined by increasing fraction of ESS and ADL score Calculated as follows: increasing fraction = (points after treatment - treatment the former points) / (100 - points before treatment) *100%
Notes	Follow-up: 21 days

Minematsu 2009

Methods	RCT: random allocation was reported but method of randomisation and concealment not reported Blinding: unclear ITT analysis: unclear Losses to follow-up: unclear
Participants	Inclusion criteria: unclear Exclusion criteria: unclear Country: Japan 808 participants (406 being assigned to the combination therapy and 402 to the monotherapy group) Comparability: background characteristics were comparable between the groups, including the baseline NIH Stroke Scale score The timing of the start of the treatment within 24 hours after stroke onset
Interventions	Treatment: argatroban plus edaravone combination therapy Control: argatroban monotherapy
Outcomes	Efficacy was determined by the proportion of modified Rankin Scale score 0 to 1 at 90 days and the frequency of SICH within the first 3 weeks
Notes	Follow-up: 90 days

Zhou 2007a

Methods	RCT: random allocation was reported but method of randomisation and concealment not reported Blinding: not reported ITT analysis: not reported Losses to follow-up: none
Participants	Inclusion criteria: start within 6 hours to 3 days, clinical diagnosis of acute ischaemic stroke (CT scan proven) Exclusion criteria: intracranial haemorrhage, simple inco-ordination or loss of consciousness, multiple organ failure, malignant tumour, BP > 180/110 mmHg Country: China 60 participants (30 treatment, 30 control) Comparability: age, sex, complications similar, more males than females Numbers of severity of stroke not reported The timing of the start of the treatment after stroke onset not reported
Interventions	Treatment: acanthopanax 80 ml once daily plus urokinase 0.1 million units twice daily for 14 days Control: basic treatment twice daily for 14 days

Zhou 2007a (*Continued*)

Outcomes	Number of participants with neurological improvement (defined by the trialists' own definition, which is similar to MESSS) at 14 days
Notes	Follow-up: 14 days

ADL: activities of daily living
BP: blood pressure
CT: computerised tomography
ESS: European Stroke Scale
ITT: intention-to-treat
MESSS: Modified Edinburgh-Scandinavian Stroke Scale
MRI: magnetic resonance imaging
NIH: National Institutes of Health
RCT: randomised controlled trial
SICH: spontaneous intracerebral haemorrhage

Characteristics of ongoing studies *[ordered by study ID]*

Goel 2009

Trial name or title	Edaravone-citicoline comparative trial in head injury and stroke
Methods	RCT ITT analysis: unclear Losses to follow-up: unclear
Participants	Inclusion criteria: presentation to hospital within 24 hours of acute head injury or ischaemic stroke; Glasgow Coma Scale less than 8 in case of normal CT after head injury Exclusion criteria: patients already had been given piracetam or thrombolytic agent; patients with haemorrhagic lesion; patients who required surgical intervention; patients with recurrent stroke; patient likely to die within 72 hours Country: India
Interventions	Patients will be randomised into 3 groups. First group will be treated with edaravone (Group-E), second with citicoline (Group-C) and third will be a control group (Group-W). Standard dose schedule for edaravone and citicoline will be used according to older studies: edaravone in doses of 30 mg 12-hourly as intravenous infusion over 60 minutes for 14 days and oral citicoline 500 mg twice-daily for 6 weeks
Outcomes	Modified Rankin Scale, Glasgow Coma Scale and National Institutes of Health Stroke Scale at admission and again at 90 days
Starting date	2007

Goel 2009 (*Continued*)

Contact information	Manish Mittal MD, Room No - 42, Neurology Department, Himalayan Institute, Swami Ram Nagar, Doiwala Dehradun - 248140, India drmanishmittal123@gmail.com; contact email: goeld007in@yahoo.co.in
Notes	

Mitsubishi Tanabe 2010

Trial name or title	Safety and pharmacokinetics of MCI-186 in patients with acute ischaemic stroke
Methods	Allocation: randomised Control: placebo Endpoint classification: safety study Intervention model: parallel assignment Masking: double-blind (patient, caregiver, investigator, outcomes assessor) Primary purpose: treatment
Participants	Inclusion criteria: full functional independence prior to the present stroke (as evidenced by a pre-morbid modified Rankin Scale score of 0 to 2), clinical diagnosis of acute stroke with CT scan ruling out intracranial haemorrhage, onset of symptoms within 1 to 24 hours of commencement of infusion of study drug, measurable deficit on NIHSS (as evidenced by a score of 3 to 15), full consciousness (i.e. the score for NIHSS item 1a = 0), written valid informed consent is obtained from the patient or next of kin or legal representative if the patient is fully conscious (i.e. the score for NIHSS item 1a = 0) but unable to read and/or sign the ICF, in accordance with National legislation and local IRB requirements Exclusion criteria: patients who are unlikely to complete the infusion of investigational product and/or are unlikely to undergo active medical management during that period due to a severe clinical condition, patients with severe illness with life expectancy less than 6 months, body weight in excess of 120 kg, patients who have received rTPA or other thrombolytics (e.g. urokinase, streptokinase, reteplase, tenecteplase) within the previous 24 hours, likelihood of forbidden concomitant therapy such as vascular surgery, coronary artery bypass graft (CABG), valve replacement or carotid endarterectomy (CEA), evidence of cerebral herniation, patients with confounding neurological diseases such as dementia, patients with CADASIL, Moyamoya or carotid dissection, patients who have experienced a stroke within the previous 3 months (Note: patients who have recently experienced a TIA, but whose premorbid mRS prior to their stroke is 0 to 2, will be allowed to enter the study), evidence from admission imaging tests of infarction involving > 1/3 of MCA territory, or entire ACA territory involvement, or internal carotid artery (ICA) occlusions without coexisting separate occlusion of the middle cerebral artery (because of the difficulty distinguishing between chronic and acute ICA lesions in such patients), pathology other than cerebral infarction on any admission imaging tests (e.g. ICH or SAH, AVM, cerebral aneurysm or cerebral neoplasm), current or previous known excessive alcohol use or dependence, current known illicit drug use or dependence, participation in a previous clinical study within 30 days, patients unlikely to be able and willing to attend all study follow-up visits, any other conditions which in the opinion of the investigator deem the patient ineligible for inclusion, females who are pregnant or intend to become pregnant or patients (male and female) who do not agree to use effective contraception for 3 months after end of treatment
Interventions	MCI-186: experimental Intervention: drug: MCI-186 Placebo: placebo comparator Intervention: drug: placebo

Mitsubishi Tanabe 2010 (*Continued*)

Outcomes	MCI-186: experimental Intervention: drug: MCI-186
Starting date	February 2009
Contact information	ClinicalTrials.gov identifier: NCT00821821
Notes	

ACA: anterior cerebral artery
AVM: arteriovenous malformation
CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CT: computerised tomography
GCS: Glasgow Coma Scale
ICF: informed consent form
ICH: intracerebral haemorrhage
IRB: Institutional Review Board
ITT: intention-to-treat
MCA: middle cerebral artery
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial
rTPA: recombinant tissue plasminogen activator
SAH: subarachnoid haemorrhage
TIA: transient ischaemic attack

DATA AND ANALYSES

Comparison 1. Edaravone versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement of neurological deficit at the end of treatment	3	496	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.60, 2.49]
1.1 MRS	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [1.19, 4.24]
1.2 ESS	2	246	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.54, 2.43]

Comparison 2. Death from all causes within the first two weeks of treatment, and during the whole follow-up period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes within the first two weeks of treatment, and during the whole follow-up period	1	250	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.22, 2.91]

Analysis 1.1. Comparison 1 Edaravone versus control, Outcome 1 Improvement of neurological deficit at the end of treatment.

Review: Edaravone for acute ischaemic stroke

Comparison: 1 Edaravone versus control

Outcome: 1 Improvement of neurological deficit at the end of treatment

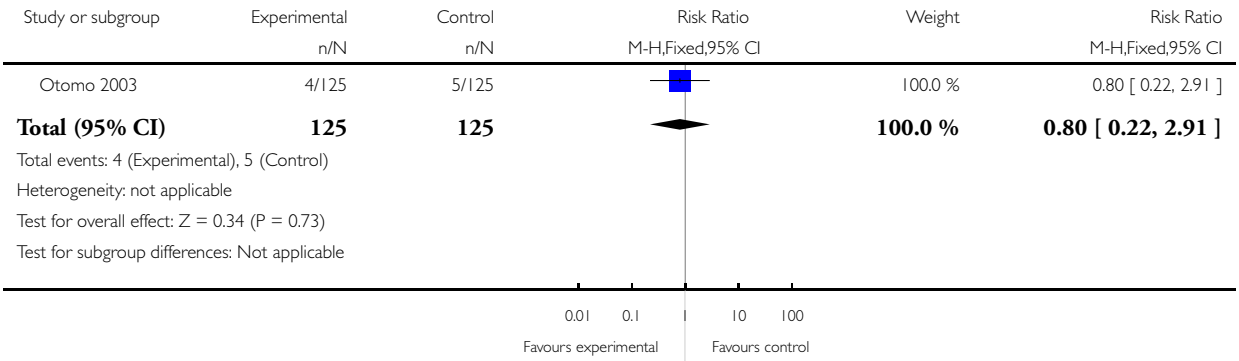
Study or subgroup	Edaravone n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 MRS					
Otomo 2003	27/125	12/125		19.2 %	2.25 [1.19, 4.24]
Subtotal (95% CI)	**125**	**125**		**19.2 %**	**2.25 [1.19, 4.24]**
Total events: 27 (Edaravone), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.51 (P = 0.012)					
2 ESS					
Zhang 2007	78/100	38/102		60.1 %	2.09 [1.59, 2.75]
Zhou 2007	19/22	13/22		20.8 %	1.46 [0.99, 2.15]
Subtotal (95% CI)	**122**	**124**		**80.8 %**	**1.93 [1.54, 2.43]**
Total events: 97 (Edaravone), 51 (Control)					
Heterogeneity: Chi?? = 2.35, df = 1 (P = 0.13); I?? =57%					
Test for overall effect: Z = 5.66 (P < 0.00001)					
Total (95% CI)	**247**	**249**		**100.0 %**	**1.99 [1.60, 2.49]**
Total events: 124 (Edaravone), 63 (Control)					
Heterogeneity: Chi?? = 2.75, df = 2 (P = 0.25); I?? =27%					
Test for overall effect: Z = 6.07 (P < 0.00001)					
Test for subgroup differences: Chi?? = 0.20, df = 1 (P = 0.66), I?? =0.0%					

Analysis 2.1. Comparison 2 Death from all causes within the first two weeks of treatment, and during the whole follow-up period, Outcome 1 Death from all causes within the first two weeks of treatment, and during the whole follow-up period.

Review: Edaravone for acute ischaemic stroke

Comparison: 2 Death from all causes within the first two weeks of treatment, and during the whole follow-up period

Outcome: 1 Death from all causes within the first two weeks of treatment, and during the whole follow-up period



APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
4. tia$1.tw
5. 1 or 2 or 3 or 4
6. (edaravon$ or norphenazone or MCI-186 or MCI186 or N demethylphenazone or norantipyrine or radicut).tw.
7. 3-methyl-1-phenyl-2-pyrazolin-5-one.tw.
8. 1-phenyl-3-methyl-2-pyrazolin-5-one.tw.
9. Antipyrine/aa [Analogs & Derivatives]
10. 6 or 7 or 8 or 9
11. 5 and 10
12. limit 11 to humans

Appendix 2. EMBASE (Ovid) search strategy

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. stroke patient/ or stroke unit/
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
4. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
5. tia$1.tw.
6. 1 or 2 or 3 or 4 or 5
7. Norphenazone/
8. (edaravon$ or norphenazone or MCI-186 or MCI186 or N demethylphenazone or norantipyrine or radicut).tw.
9. 3-methyl-1-phenyl-2-pyrazolin-5-one.tw.
10. 1-phenyl-3-methyl-2-pyrazolin-5-one.tw.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. limit 12 to human

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 12, 2011

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: Feng Shejun, Yang Qingwei, Liu Ming
- Develop the search strategy: Feng Shejun, Li Weizheng, Yuan Wenming
- Search for trials: Feng Shejun, Li Weizheng, Yuan Wenming
- Obtain copies of trials: Feng Shejun, Li Weizheng, Yuan Wenming
- Select trials for inclusion: Feng Shejun, Li Weizheng, Liu Ming
- Extract data: Feng Shejun, Li Weizheng
- Enter data into RevMan: Feng Shejun, Li Weizheng
- Carry out the analysis: Feng Shejun, Li Weizheng
- Interpret the analysis: Feng Shejun, Liu Ming
- Draft the final review: Feng Shejun, Yang Qingwei, Liu Ming, Li Weizheng, Zhang Shihong, Wu Bo, Yuan Wenming, Li Juntao
- Update the review: Feng Shejun, Yuan Wenming, Yang Qingwei

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, China.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antipyrine [*analogs & derivatives; therapeutic use]; Brain Ischemia [complications]; Free Radical Scavengers [therapeutic use]; Neuroprotective Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy; etiology]

MeSH check words

Humans