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Safety of edaravone in acute ischemic stroke: A systematic review and meta-analysis

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Abstract

Background & Objective: Stroke is a major cause of death and disability, however many patients do not benefit from time-limited reperfusion therapies. Edaravone is a neuroprotective agent that has been shown to improve neurologic impairment after ischemic stroke. This paper aims to review and synthesize evidence on the safety of edaravone in acute ischemic stroke. *Methods:* This is a systematic review and meta-analysis of randomized controlled trials and observational studies on the use of edaravone with standard stroke treatment, versus standard stroke treatment alone, among patients with acute ischemic stroke. Mortality was regarded as the primary outcome. Secondary outcomes of interest were other neurologic safety outcomes (intracerebral hemorrhage, hemorrhagic transformation) and systemic safety outcomes (renal and hepatic impairment, other adverse drug reactions).
Results: 15 studies were included. The total number of study participants was 15,654, with 81.5% given edaravone and 18.4% given control. Overall, edaravone treatment was associated with a significantly reduced risk of mortality compared to control (RR 0.63, p<0.00001, 0.95% CI 0.52-0.75). Among ischemic stroke patients given reperfusion therapy, edaravone treatment was associated with lower risk of intracerebral hemorrhage (RR 0.77, 95% CI 0.32-1.84), symptomatic intracerebral hemorrhage (RR 0.55, 95% CI 0.16-1.84) and hemorrhagic transformation (RR 0.68, 95% CI 0.32-1.41), however results were not statistically significant.
Conclusions: Current evidence suggests that the use of edaravone in addition to standard treatment among patients with acute ischemic stroke is associated with lower risk of mortality. Larger high-quality trials outside Asia with longer length of follow-up are recommended for further investigation.

Keywords: Edaravone, safety, ischemic stroke, stroke, mortality

INTRODUCTION

Stroke remains the second leading cause of death after ischemic heart disease, and the third leading cause of disability.[1] In 2019, there were 143 million disability adjusted life years (DALYs) lost due to stroke.[1] It is a disease with a high public health and financial burden, particularly in low-income countries.[2–4] At present, the only proven treatments to recover brain tissue at risk in acute ischemic stroke are intravenous thrombolysis with recombinant tissue plasminogen activator (rTPA, or alteplase) within 4.5 hours of ischemic stroke onset[5,6], and more recently endovascular thrombectomy up to 24 hours.[7,8] Beyond these time windows, only medication for secondary stroke prevention can be given.[9] Moreover, access to these essential treatments may be limited especially in low-income countries due to social barriers to healthcare.[2,3] It is therefore beneficial to study other promising and easily accessible strategies to improve stroke recovery such as neuroprotective agents.

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a novel free radical scavenger produced by Mitsubishi Tanabe Pharma Corporation (Japan).[10] It was synthesized via condensation of hydrazine and 3-oxo-propionic esters in refluxed ethanol.[10] The compound has lipophilic substituents, causing it to be a potent inhibitor of lipid peroxidation[10,11], and at physiologic pH its anionic form reacts strongly with reactive oxygen species in the ischemic brain.[11–13] It was first discovered to have a beneficial effect in animal models of stroke by Japanese researchers in the 1980s, with studies showing improvement in terms of functional outcome and infarct volume.[14] Subsequent experimental studies showed that the

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neuroprotective properties of edaravone are due to its antioxidant effects, inhibiting proinflammatory responses after brain ischemia[10], while decreasing brain edema and oxidative injury.[12,13] Clinical trials have since been conducted in Japan and China on the use of edaravone among patients with acute ischemic stroke of different etiologies, showing benefit in terms of functional recovery.[13,15] Two Cochrane meta-analyses concluded that edaravone may improve neurologic impairment after acute ischemic stroke[15] and intracerebral hemorrhage (ICH)[16], but both recommend larger and higher quality trials for further investigation. Two recent meta-analyses published over the past year showed that edaravone treatment was associated with improved neurologic outcomes at 90-day follow up.[17,18] In the current Japanese guidelines for treatment of ischemic stroke, edaravone is the only neuroprotective agent recommended, with a Grade B level of evidence.[19]

At present, the use of edaravone is gradually expanding to countries outside Japan. A comprehensive review of the safety of this novel medication is therefore timely and warranted. The objective of this paper is to review and synthesize the evidence on the safety of edaravone as a neuroprotective agent in addition to standard stroke therapy in acute ischemic stroke, in terms of mortality, neurologic safety outcomes, and other adverse drug reactions.

METHODS

Search strategy

Searches were conducted in the following scientific databases: PubMed, the Cochrane Library, and Google Scholar. The following keywords were used: "edaravone", "stroke", and "safety". Duplicate terms included "MCI-186", "side effects", "adverse events", "tolerability", "infarct", "ischemic stroke", "cerebral infarction", "brain infarction", and "cerebrovascular disease".

During search of the PubMed and Cochrane Library databases, the following filters were applied: type of study (cohort studies, clinical trials, and randomized controlled trials), date of publication (database inception up to September 15, 2022), language (English), and study subjects (human adults aged 18 years and older).

Eligibility criteria

Studies were considered eligible if they investigated the use of edaravone with standard stroke treatment, versus standard stroke treatment alone, among patients with acute ischemic stroke aged 18 and older, of any race or ethnicity, which were published from inception up to September 15, 2022. Study designs were limited to published observational cohort studies, clinical trials, and randomized controlled trials. Studies were included regardless of dose or duration of edaravone administration but were limited to the intravenous preparation of edaravone. Trials that compared a combination of edaravone and reperfusion therapy, either with alteplase or endovascular thrombectomy, were also included these are also part of standard stroke treatment.

Any of the following should be among the study outcomes in the included studies: a) mortality or death at any point during the study, either in-hospital or during follow-up; b) neurologic safety outcomes, which include ICH, symptomatic ICH, hemorrhagic transformation, or stroke progression; c) systemic safety outcomes such as renal or hepatic impairment, or other adverse drug reactions.

Studies were excluded if edaravone was not compared to a placebo or control group, and if edaravone was compared to or combined with other neuroprotective agents, other edaravone compounds, or other experimental medications for acute stroke. Trials using edaravone that were conducted among populations already with significant renal or hepatic impairment were also excluded. Studies not in English, animal studies, clinical trial protocols, unfinished and unpublished trials were excluded. Studies not from primary literature such as review articles, editorials, commentaries, or meta-analyses were likewise excluded.

Selection process

After removal of duplicates, studies resulting from the initial search were screened for eligibility through their titles and abstracts by the primary investigator (SPB). Studies that were obviously not relevant to the objectives of this review were excluded. A second and third round of screening were performed by both authors (SPB and JCN) independently based on abstract and full text, after which the list of studies to be included in the systematic review was finalized. References identified during the second and third rounds of screening were downloaded through a reference management software (Mendeley Reference Manager version 2.77.0). To ensure comprehensiveness, reference lists of included studies as well as other previously published meta-analyses were cross-checked for additional studies that would meet the eligibility criteria.

Outcomes assessed

Data items extracted included the following: general information (author, year of publication, country) and study characteristics in terms of study design, population, demographic characteristics of study participants, interventions used, time window of edaravone administration, dose and duration of edaravone given, baseline stroke severity in terms of National Institutes of Health Stroke Scale (NIHSS), and outcome measures.

Mortality was regarded as the primary outcome, whether this was expressed as in-hospital mortality or a modified Rankin Scale (mRS) of 6 at follow-up. Secondary outcomes were other neurologic safety outcomes (ICH, hemorrhagic transformation, stroke progression) and systemic safety outcomes (renal or hepatic impairment, other adverse drug reactions).

These outcomes were compared between the edaravone group (those given edaravone in addition to standard therapy, with or without alteplase or endovascular thrombectomy) versus the control group (those given standard therapy only, with or without alteplase or endovascular thrombectomy).

Hemorrhagic transformation was defined using the European Cooperative Acute Stroke Study II (ECASS II) criteria and included any of the following types: hemorrhagic infarction type 1, hemorrhagic infarction type 2, parenchymal hematoma type 1, and parenchymal hematoma type 2.[6] Symptomatic ICH was defined using criteria from the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): a 4-point increase in NIHSS score from baseline or death within 36 hours, and local or remote parenchymal hemorrhage type 2 on neuroimaging, with a dense hematoma >30% of the lesion volume with significant space-occupying effect.[20] Stroke progression was defined as a 4-point increase in NIHSS score from baseline.[21] Adverse drug reactions were defined according to the World Health Organization reaction terminology as any other appreciable harmful or unpleasant symptom or reaction resulting from treatment with edaravone or control and may be related to their use.[22]

Data analysis

A pre-specified electronic data collection sheet was used for all included studies to retrieve pertinent information such as study characteristics, population studied, intervention (edaravone dosage and route) and study outcomes. Statistical analysis and risk of bias assessments were performed via Review Manager version 5.4.1. The effect measure of interest was expressed in terms of risk ratio (RR) with 95% confidence interval and pooled using the Mantel-Haenszel estimator for random effects. Heterogeneity was measured using the I2 statistic, with values ≥50% considered significant. Publication bias was assessed using funnel plots. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 statement guidelines.[23] This study was approved by the Institutional Review Board of the authors' institution.

RESULTS

Characteristics of the retrieved studies

Figure 1 shows the PRISMA flow diagram of the study selection. A total of 279 articles were identified after the initial search (39 from PUBMED, 115 from Cochrane Library, and 125 from Google Scholar). After removal of duplicates, experimental and animal studies, case reports, unpublished or unavailable studies, study protocols, non-English studies, reviews, commentaries and meta-analyses, 124 studies were assessed for eligibility via their title and abstract. Studies were further excluded if edaravone was compared to other neuroprotective drugs or combined with other experimental interventions for stroke, if other edaravone compounds were used such as edaravone dexborneol, if edaravone was not the intervention for studies on stroke, and if edaravone was used in other conditions aside from ischemic stroke. Finally, a third round of screening based on full text was performed on 29 articles. 6 articles were excluded since they did not report on any mortality or safety outcomes, 4 studies excluded since the study population already had baseline significant renal and hepatic impairment, and 4 studies excluded since edaravone was not compared to a placebo or control group. 15 studies were included in the final review.

Characteristics of included studies are presented in Table 1.

Study designs

The included studies were published from 2003-2019. Among these, seven were retrospective cohort studies, five were randomized controlled trials, two were open-label trials, and one was a historical-controlled trial.

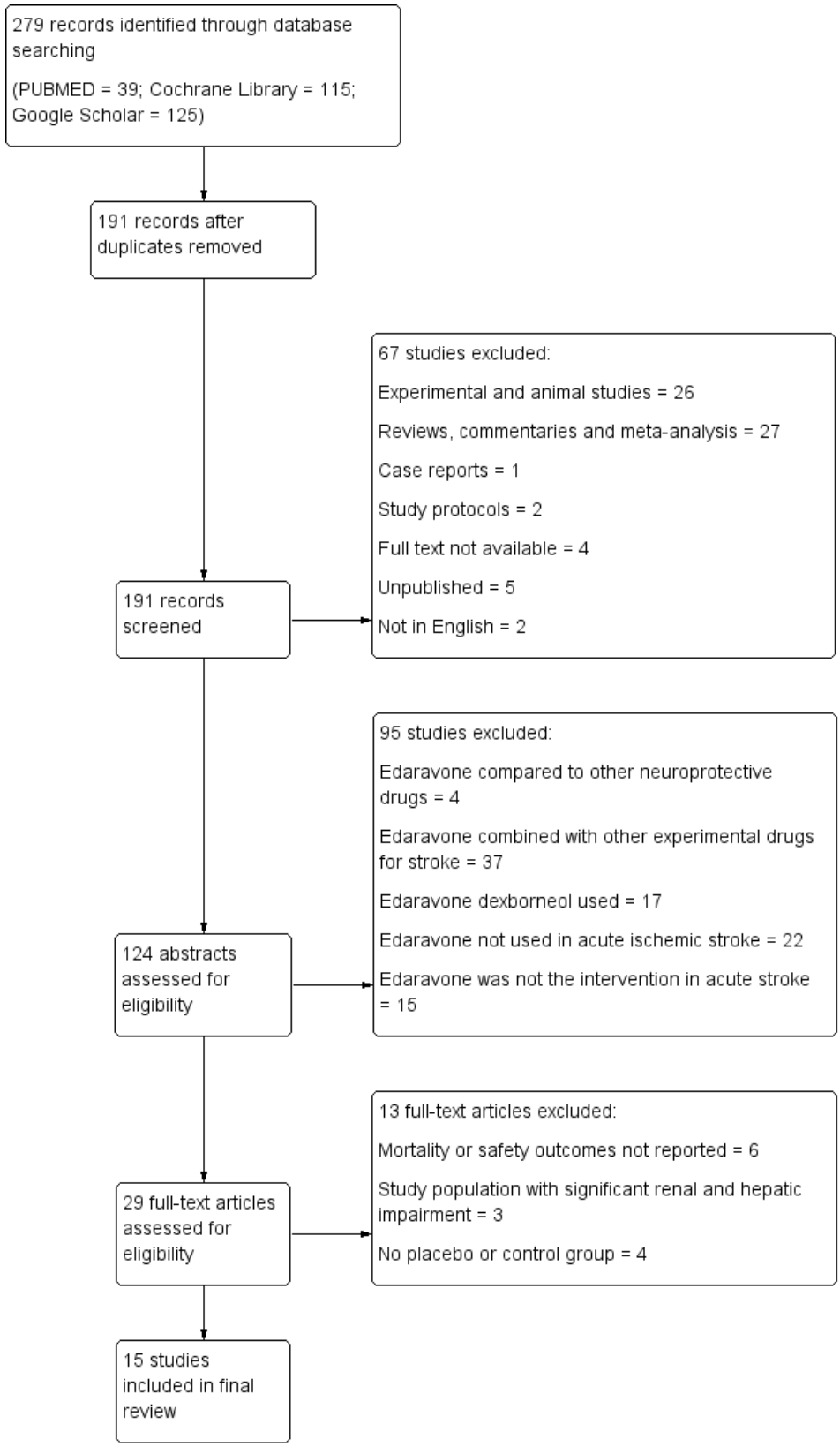

Figure 1. PRISMA flow diagram of the study selection.

TABLE 1: Characteristics of studies included in the review

Author, year	Country	Study type	Population studied	Sample size (T/C)	Therapeutics		Mean age in years (T/C)	Sex, males (T/C)	Baseline NIHSS (mean, range)		Time window (hrs)†	Dose of edaravone	Treatment duration (days)	Primary outcomes	Safety outcomes	Follow up duration (days)
					T	C			T	C						
Enomoto, 2019[24]	Japan	Retro-spective cohort	Ischemic stroke patients given alteplase and endovascular therapy	10,281/1227	E+A+ EVT	A+EVT	75/79	5924/675 58%/55%	NR	NR	≤ 48	30mg bid	3-14	mRS	Mortality in-hospital, ICH	Upon discharge
Inatomi, 2006[25]	Japan	Historical controlled trial	Cardioembolic stroke patients, onset within 7 days	141/101	E+R±A	R±A	78/77	67/48 48%/48%	16	15	≤ 24	30mg bid	7	NIHSS, mRS	Mortality <6mo	Upon discharge, 180
Ishibashi, 2013[26]	Japan	Retro-spective cohort	Ischemic stroke patients, onset within 48h	237/388	E+R	R	77‡ (36-101)	331 53%‡	NR	NR	≤ 24	30mg bid	14	mRS	Mortality in-hospital	Upon discharge
Kaste, 2013[27]	Finland Nether-lands UK	RCT	Ischemic stroke patients, onset within 24h	25/11	E+R	R	64.5/69	19/8 76%/72%	5 (3-9)	6 (4-12)	NR	0.08-0.16 mg/kg LD + 0.2-0.4 mg/kg/h infusion	3	mRS, BI	Adverse drug reactions	3, 5, 31, 87
Kimura, 2012[28]	Japan	Random-ized open label trial	Ischemic stroke patients with MCA M1 or M2 occlusion	23/17	E+A± EVT	A±EVT	76.9/75.8	9/14 39%/82%	12.7±6.4	12.8±6.4	≤ 3	30mg bid	7	NIHSS, recanaliza-tion	HT, sICH, stroke progression	1
Kono, 2013[29]	Japan	Retro-spective cohort	Ischemic stroke patients aged <80y and >80y	118/11	E+A+R	A+R	72.4/82.5	65/3 55%/27%	12 (5-17)	17 (15-19)	≤ 3	NR	NR	NIHSS, mRS, infarct size, recanaliza-tion	aICH, sICH, bleeding	7, 90
Lee, 2018[30]	China	Retro-spective cohort	Ischemic stroke patients	132/136	E+A+R	A+R	71.9/74.05	61/67 46%/49%	20.88 ± 8.31	20.67 ± 10.06	≤ 24	30mg bid	14	NIHSS, BI, mRS	Mortality <7d, HT, aICH, sICH, bleeding	7, 14, upon discharge
Li, 2020[31]	China	RCT	Ischemic stroke patients, onset within 48h	48/48	E+R	R	60.5/62.5	25/29 52%/60%	26.06± 5.23	27.08± 5.68	≤ 48	30mg bid	14	NIHSS, TNF-alpha, IL-8, ADL	Adverse drug reactions	14

Miyaji, 2015[32]	Japan	Retro-spective cohort	Ischemic stroke patients with large vessel occlusion, onset within 24h	1129/313	E+A+ EVT	A+EVT	73.2/76.9	632/178 56%/57%	15.5 ± 8.3	15.9 ± 9.4	≤ 24	30mg bid	7	mRS, NIHSS	-	90
Otomo, 2003[33]	Japan	RCT	Ischemic stroke patients, onset within 72h	125/125	E	P	66.3/66.1	82/83 66%/67%	NR	NR	≤ 72	30mg bid	14	mRS	Adverse drug reactions	Upon discharge, 90
Sharma, 2011[34]	India	Random-ized open-label trial	Ischemic stroke patients, onset within 6-72h	25/25	E+R	P+R	58.12/56.0	16/15 64%/60%	10.56 ± 5.74	10.08 ± 5.66	≤ 72	30mg bid	14	mRS, BI	Adverse drug reactions	14, 30, 90
Sun, 2019[35]	China	RCT	Ischemic stroke patients	65/65	E+R	R	52.4/51.3	37/40 57%/6 1%	22.20±8.03	22.25±9.01	NR	30mg bid	14	NIHSS, BI	Adverse drug reactions	14
Toyoda, 2004[36]	Japan	Retro-spective cohort	Ischemic stroke patients with ICA occlusion, onset within 6h	30/31	E+R	R	77/77	15/11 50%/35%	21 ± 4	21 ± 3	≤ 6	30mg bid	14	Infarct volume, midline shift, mRS	Mortality <14d, HT	60
Wada, 2014[37]	Japan	Retro-spective cohort	Ischemic stroke patients, onset within 3h	356/356[d]	E+A+R	A+R	Edaravone group: 80-89y (43.5%) Control group: 80-89y (40.2%)	196/199 55.1%/56.7%	NR	NR	≤ 24	30mg bid	14	mRS	Mortality <7d, ICH, length of stay	Upon discharge
Zheng, 2016[38]	China	RCT	Ischemic stroke patients with diabetes, onset within 24h	35/30	E+R	R	63.4/59.8	20/16 57.1%/53.3	14.8±3.5	14.0±3.9	≤ 24	30mg bid	14	NIHSS, BI	HT, infec-tion, stroke progression, epilepsy	7, 14

Abbreviations:
T = treatment group; C = control group; A = alteplase; EVT = endovascular thrombectomy; E = edaravone; R = routine stroke therapy; P = placebo; RCT = randomized controlled trial; ICA = internal carotid artery; MCA = middle cerebral artery; NSAIDS = non-steroidal anti-inflammatory drugs; d = days; NR = not reported; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; BI = Barthel Index; HT = hemorrhagic transformation; ICH = intracerebral hemorrhage; aICH = asymptomatic intracerebral hemorrhage; sICH = symptomatic intracerebral hemorrhage; TNF-alpha = tumor necrosis factor alpha; IL-8 = interleukin-8; ADL = activities of daily living scale
[†]Number of hours post ictus of edaravone administration
[‡]Mean age and sex for edaravone vs non-edaravone group were not reported

Patient characteristics

The total number of study participants was 15,654. A total of 8,885 (56.8%) were males. 12,770 (81.5%) were given edaravone, while 2,884 (18.4%) were in the control group. Those in the edaravone group had a mean age of 70.1, while those in the control group had a mean age of 71.2. Patient ethnicity was mostly Asian, with nine studies conducted in Japan,[24-26,28,29,32,33,36,37] four in China,[30,31,35,38] and one in India.[34] The only non-Asian study was a multicenter randomized controlled trial conducted in Finland, Netherlands and the United Kingdom.[27]

The largest study was a retrospective cohort study using data from the Japanese Diagnosis Procedure Combination database,[24] which contributed 73.5% of the study population. Another study used this same database, the two studies had different populations – the larger study was done on patients given both alteplase and endovascular thrombectomy,[24,37] while the other was done on patients given alteplase only.[37]

Eight studies compared edaravone with routine therapy versus routine therapy alone,[25–27,31,34-36,38] four studies compared edaravone with alteplase and routine therapy versus alteplase and routine therapy alone,[25,29,30,37] three compared edaravone with alteplase with or without endovascular thrombectomy,[24,28,32] and one compared edaravone versus placebo.[33] Routine therapy consisted of other medications such as antiplatelets or anticoagulants for secondary stroke prevention, antihypertensives, and statins. Most studies excluded patients with baseline renal or hepatic dysfunction. Other notable exclusion criteria were coma,[30,33,35,37] previous history of stroke or mental disease,[26,31,34,35] pre-stroke mRS >2,[27,30] other serious comorbidities or malignancies,[26,27,31,34,38] pregnancy or lactation,[24,34] and current infection or antibiotic use.[27,30,31,38]

Most studies were conducted among patients with moderate to severe stroke with mean NIHSS scores of 12-26.[25,28–32,34-36] Only one study was conducted among patients with mild to moderate ischemic stroke, with mean NIHSS scores of 5-6 (range 3-12).[27] Three studies were among patients with large vessel occlusion,[28,32,36] hence alteplase was included as part of routine stroke therapy at the investigator's discretion, along with endovascular thrombectomy[32] or decompressive hemicraniectomy[36] if these were warranted. Four studies did not report baseline stroke severity; instead, three of these reported baseline Japan Coma Scores (JCS) on admission.[24,26,33,37]

Edaravone was given via the intravenous route, most commonly using dose of 30 mg twice a day for 3 up to 14 days. Only one study prescribed a dosing regimen per kilogram weight with a loading dose followed by infusion.[27] One study did not report edaravone dose.[29] Edaravone was administered within 24 up to 72 hours after stroke onset, with some investigators[29,36] opting to administer it right after alteplase infusion.

All studies had functional outcome (expressed via the mRS score either upon discharge or at follow up) as their primary endpoint. A favorable outcome was defined as mRS 0-2.

Mortality outcomes

The mortality outcomes across studies included in the review are shown in Figure 2. Five studies recorded mortality at 90-day follow up as an mRS score of 6.[27,29,32-34] Data on in-hospital mortality outcomes were available from 3 studies,[24–26] while data on mortalities within 7-14 days were available from 3 studies.[30,36,37] Only the study by Kaste recorded no mortalities at 90 day follow up. One study recorded mortality at 6 months.[25]

In the edaravone group, 1269 out of 12,740 patients died, while in the control group 437 out of 2,839 patients died. Overall, there were less mortalities observed in the edaravone group compared to the control group (9.9% vs 15.4%). The pooled estimate shows that edaravone treatment was associated with a significantly reduced risk of mortality compared to control (RR 0.63, p<0.00001, 0.95% CI 0.52-0.75), with low heterogeneity regardless of study design (I^2 = 32%).

Similar findings were observed in the studies with the largest population (RR 0.57, 95% CI 0.50-0.65)[24] and the oldest population (RR 0.67, 95% CI 0.45-0.99).[37] Similarly, risk of mortality was lower for the edaravone group compared to control during in-hospital follow up (RR 0.69, 95% CI 0.39-1.20), within 7-14 days after stroke (RR 0.67, 95% CI 0.45-0.99), within 90 days (RR 0.55, 95% CI 0.44-0.70), and within 180 days (RR 0.52, 95% CI 0.31-0.89).

Only the study by Otomo reported the specific causes of death. The 4 mortalities in the edaravone group (reported as mRS 6 at 90 days) were attributed to progression of brain infarction, sudden cardiac arrest, pneumonia, and suicide due to mental depression. None were judged to be related to the test drug.[33] The 5 mortalities in the control group were attributed to progression of brain infarction, tonsillar herniation, pneumonia,

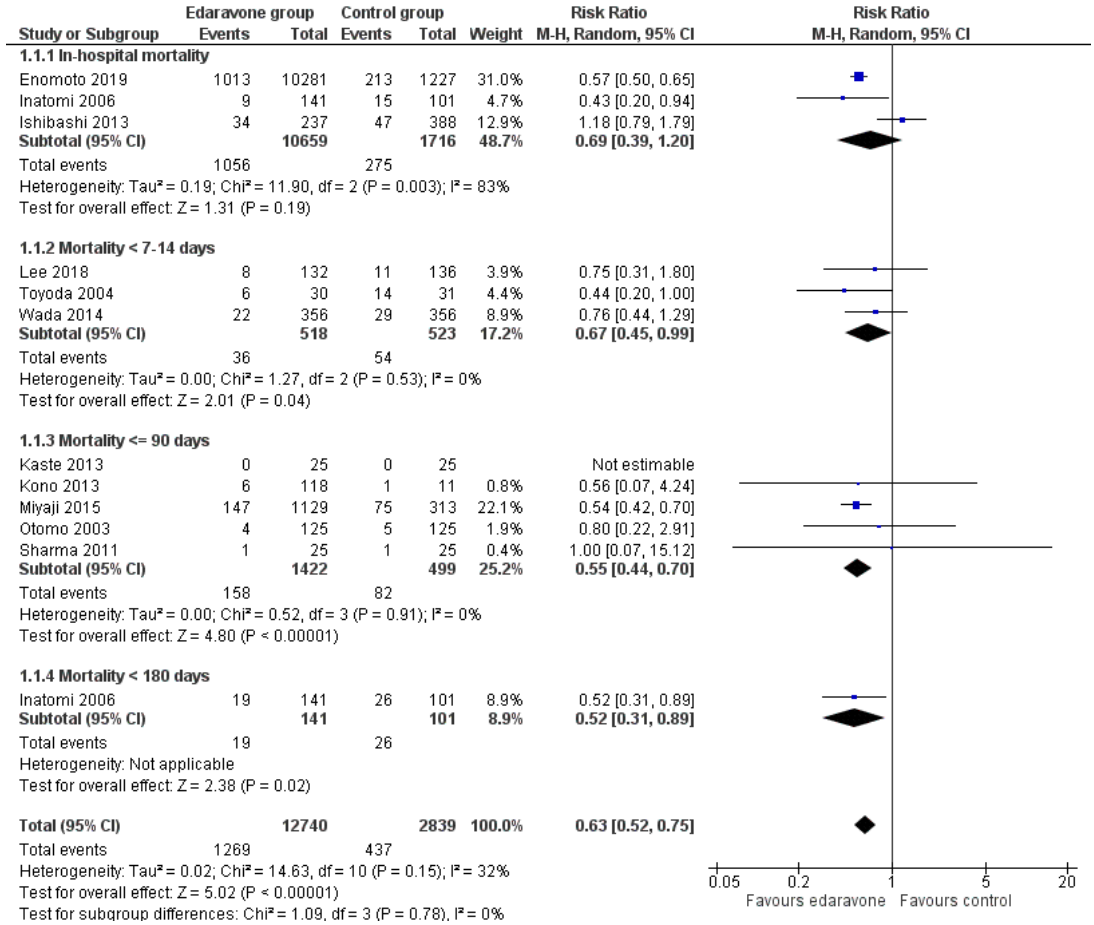

Figure 2. Forest plot of mortality outcomes among patients given edaravone versus control.

and disseminated intravascular coagulation due to liver cirrhosis.

Neurologic safety outcomes

Neurologic safety outcomes across studies are shown in Figure 3. Studies that reported on these outcomes investigated the efficacy and safety of edaravone among patients given alteplase or endovascular thrombectomy.[24,28-30,37,38] Neurologic safety outcomes included ICH (symptomatic or asymptomatic), hemorrhagic transformation, and stroke progression.

Among ischemic stroke patients given reperfusion therapy, edaravone treatment was associated with lower risk of ICH (RR 0.77, 95% CI 0.32-1.84), symptomatic ICH (RR 0.55, 95% CI 0.16-1.84) and hemorrhagic transformation (RR 0.68, 95% CI 0.32-1.41), however results were not statistically significant. Edaravone treatment was also associated with lower risk of stroke progression (RR 0.32, 95% CI 0.14-0.73), however only two small studies reported on this outcome.[28,38]

Systemic safety outcomes

Only five studies reported on systemic safety outcomes or adverse drug reactions, and those were studies that compared edaravone versus routine stroke therapy[27,31,34,35] or placebo[33] (Figure 4). There was no statistically significant difference in the risk of hepatic impairment (RR 0.48, 95% CI 0.21-1.12) and renal impairment (RR 0.58, 95% CI 0.15-2.21) between edaravone and control. Hepatic and renal impairment were described as increase in serum laboratory values (alanine aminotransferase, aspartate aminotransferase, and creatinine, respectively) but these were noted to be transient and not clinically significant.[27,33,34] In terms of all treatment-related adverse drug reactions reported across studies, there was also no statistically significant difference between edaravone and control (RR 0.84, 95% CI 0.61-1.17).

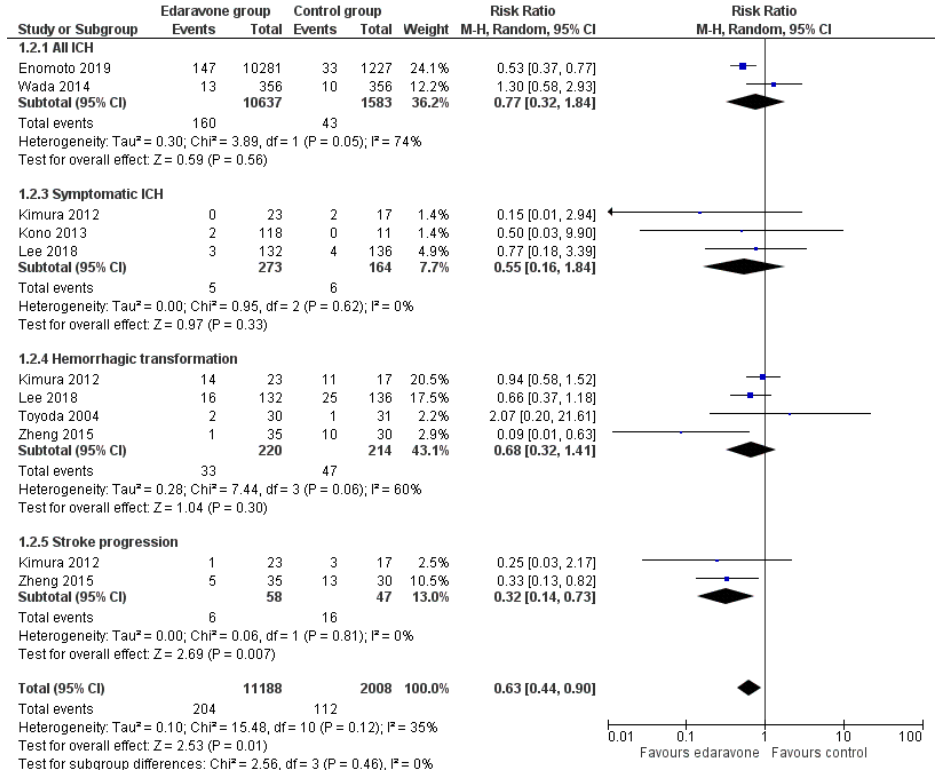

Figure 3. Forest plot of neurologic adverse outcomes among patients given edaravone versus control.

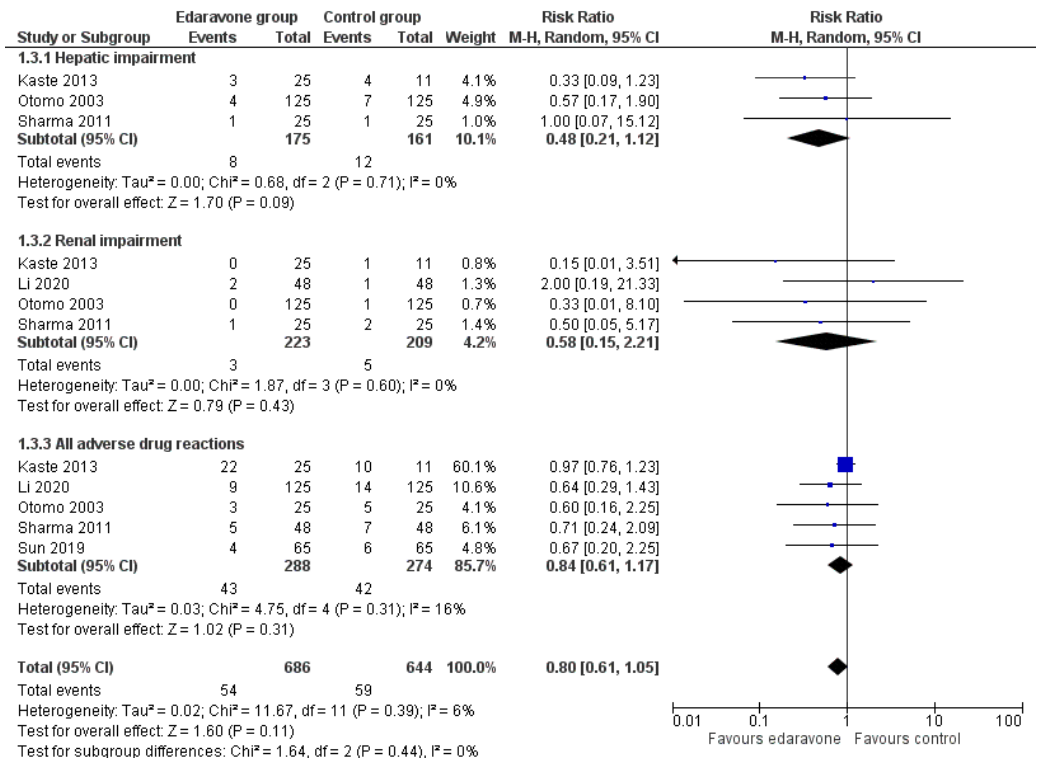

Figure 4. Forest plot of systemic adverse outcomes (hepatic and renal impairment) among patients given edaravone versus control.

Table 2 shows the frequency of other types of adverse drug reactions reported across studies. Frequently reported reactions were skin rash and pruritus (8 in the edaravone group versus 7 in the control group) and nausea (11 in the edaravone group versus 7 in the control group). The study by Kaste reported on the most variety of systemic adverse outcomes. Aside from the abovementioned, other adverse outcomes reported in this study were bradycardia, hypotension, hypertension, hyperglycemia, and infusion site reactions. Hypertension was the most frequently reported vascular adverse event, with 5 patients in the edaravone group and 4 in the control group (20% vs 36%). In the edaravone group, 2 patients developed bradycardia, 1 developed hypotension, and 2 developed hyperglycemia. None of these were observed in the control group.

Risk of bias assessment

Risk of bias was high since most studies were observational and lacked random sequence generation, allocation concealment, and blinding (Figure 5). Funnel plots show no publication bias (Figure 6).

DISCUSSION

In this systematic review, edaravone treatment in addition to standard stroke therapy was significantly shown to be associated with reduced risk of mortality compared to standard stroke

TABLE 2: Other adverse drug reactions among ischemic stroke patients given edaravone versus control

	Edaravone group (n/N, %)	Control (n/N, %)	Studies
Skin rash, pruritus	8 / 223 (3.6%)	7 / 209 (3.3%)	Kaste 2013[27] Otomo 2003[33] Sharma 2011[34] Li 2020[39]
Nausea	11 / 263 (4.2%)	7 / 249 (2.8%)	Kaste 2013[27] Otomo 2003[33] Li 2020[39] Sun 2019[40]
Diarrhea	0 / 150 (0.0%)	3 / 150 (2.0%)	Otomo 2003[33] Sharma 2011[34]
Fever	2 / 150 (1.3%)	3 / 150 (2/0%)	Otomo 2003[33] Sharma 2011[34]
Infusion site reactions	2 / 25 (8.0%)	2 / 11 (18.2%)	Kaste 2013[27]
Vomiting	1 / 65 (1.54%)	1 / 65 (1.54%)	Sun 2019[40]
Dizziness	3 / 65 (4.62%)	2 / 65 (3.08%)	Sun 2019[40]
Headache	8 / 25 (32%)	4 / 11 (36%)	Kaste 2013[27]
Bradycardia	2 / 25 (8%)	0 / 11 (0%)	Kaste 2013[27]
Hypertension	5 / 25 (20%)	4 / 11 (36%)	Kaste 2013[27]
Hypotension	1 / 25 (4%)	0 / 11 (0%)	Kaste 2013[27]
Hyperglycemia	2 / 25 (8%)	0 / 11 (0%)	Kaste 2013[27]
Herpes	0 / 48 (0%)	1 / 48 (2.08%)	Li 2020[39]
Abdominal pain	0 / 125 (0%)	1 / 125 (0.08%)	Otomo 2003[33]
Disseminated intravascular coagulation	0 / 125 (0%)	1 / 125 (0.08%)	Otomo 2003[33]
Increased LDH, WBC, serum amylase	0 / 125 (0%)	1 / 125 (0.08%)	Otomo 2003[33]

n / N, where n is the number of patients with an adverse event, and N is the study treatment group.
**Note: only articles listed under the column ("studies") reported on these outcomes.*

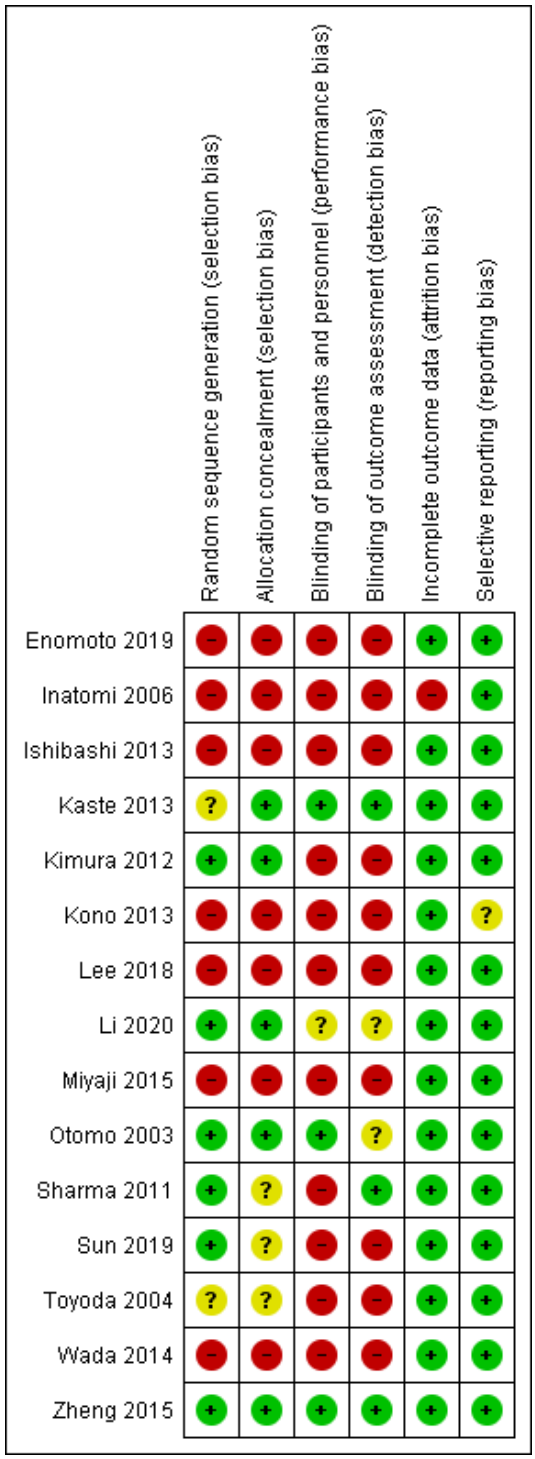

Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

therapy alone. This is comparable with other recently published data[17,18] in which a significant reduction of mortality was observed in the edaravone group compared to control. However, it should be noted that only one study in this review recorded the causes of death, and none of the mortalities were attributed to the test drug.[33]

In terms of other safety outcomes, our data showed no significant differences in terms of neurologic adverse effects (such as ICH, symptomatic ICH, hemorrhagic transformation, and stroke progression) between edaravone and control. This is comparable with the result of a recent systematic review and meta-analysis showing no association between intracerebral hemorrhage and edaravone treatment, but with high heterogeneity between studies.[18] Moreover, our data showed that edaravone treatment did not appear to significantly increase the risk of hepatic impairment, renal impairment, or other treatment-related adverse drug reactions, consistent with a recent meta-analysis including only seven randomized controlled trials.[17] Importantly, most treatment related adverse effects reported were transient and of mild to moderate severity. However, at present there are no published data on the possible long-term adverse effects of the medication since most studies limit patient follow-ups to 90 days post-stroke.

Earlier experimental studies showed that edaravone had good safety and tolerability. Preclinical animal toxicology studies showed that edaravone has no acute toxicities when a rat hepatoma cell system was used for analysis, however the drug was rapidly metabolized via cytochrome P450 enzymes.[41] The earliest human clinical study on edaravone was the 1998 phase I trial done in Japan, which investigated the safety and pharmacokinetic profile of edaravone in healthy male volunteers.[42] Edaravone at 0.2-1.5mg/kg was given via intravenous infusion for 40 minutes. Pharmacokinetic studies showed a short half-life of 0.15 – 5.16 hours, metabolism via sulfation or glucuronidation, and excretion in the urine within 24 hours of administration.[42] In this trial, edaravone was well tolerated in normal volunteers after single or multiple dose intravenous administration, with no adverse effects reported. In the phase II trial, edaravone was given to patients with acute ischemic stroke within 72 hours of ictus, showing improvement in neurologic deficits with no adverse effects noted.[10] After this study, the appropriate dose of edaravone was estimated to be 30 mg IV given as infusion over 30 minutes, twice a day, for 2 weeks. The phase III trial was a multicenter, randomized, placebo-controlled, double-blind trial with edaravone given at 30 mg IV twice a day

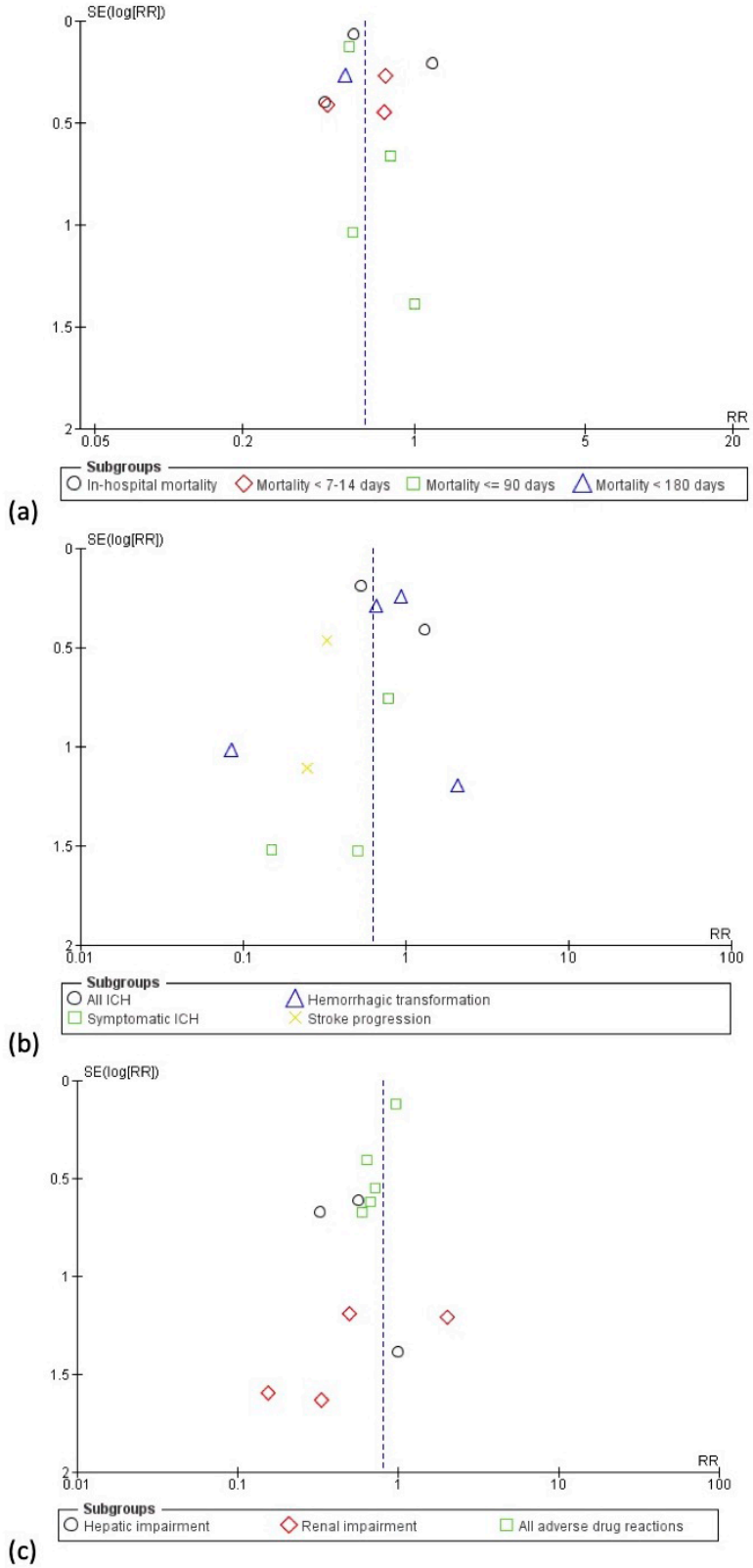

Figure 6. Funnel plots for mortality outcomes (a), neurologic safety outcomes (b), and major systemic safety outcomes (c).

for 2 weeks showing beneficial effects in terms of mRS scores among treated patients.[33] The safety outcomes from this study were included in this systematic review. Other subsequently published studies showed that among ischemic stroke patients with baseline kidney disease, there was no significant change in glomerular filtration rate after edaravone administration,[43,44] and edaravone may be protective against acute kidney injury.[45] However, a study conducted among patients with liver injury and acute ischemic stroke showed that edaravone-related liver injury accounted for 20% of evaluated patients, and most showed increases in serum aminotransferases within 7-10 days after drug administration which resolved within 10-14 days.[46]

There are several limitations to our study. Majority of data are derived from observational studies, which inherently have a high risk of bias due to lack of randomization, allocation concealment, and blinding. Moreover, only one retrospective cohort study contributed to more than half of the patient population. Third, almost all included studies were limited to populations from Japan or China. This affects external validity of the study results and may limit its generalizability to other ethnic populations. The study authors therefore suggest that larger well-designed randomized controlled trials outside Asia be conducted, with longer length of follow ups. Finally, only published articles in English were included in this review, which may contribute to information bias.

In conclusion, currently available evidence suggests that the use of edaravone in addition to standard treatment among patients with acute ischemic stroke is safe and may be associated with reduced risk of mortality. Larger high-quality trials outside Asia with longer length of follow-up are recommended for further investigation.

DISCLOSURE

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Conflicts of interest: None

Ethics statement: This study was approved by the Institutional Review Board of Jose R. Reyes Memorial Medical Center. Since this is a systematic review, there are no risks to subjects involved, and informed consent was waived.

REFERENCES

1. Feigin VL, Stark BA, Johnson CO, *et al*. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0.
2. Collantes MEV, Miel Y, Zuñiga H, Uezono DR. Incidence and prevalence of stroke and its risk factors in the Philippines: A systematic review. *Acta Medical Philippina* 2022;54(14):26-34. doi:10.47895/amp.vi0.1753.
3. Collantes MEV, Zuñiga YH, Granada CN, *et al*. Current state of stroke care in the Philippines. *Front Neurol* 2021;12:1-7. doi:10.3389/fneur.2021.665086.
4. Navarro JC, Baroque AC, Lokin JK, Venketasubramanian N. The real stroke burden in the Philippines. *Int J Stroke* 2014;9(5):640-1. doi:10.1111/ijs.12287.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Eng J Med* 1995;333(24):1581-7. doi:10.1056/NEJM199512143332401
6. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Eng J Med* 2008;359(13):1317-29. doi:10.1056/nejmoa0804656.
7. Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Eng J Med* 2018;378(8):708-18. doi:10.1056/nejmoa1713973.
8. Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Eng J Med* 2018;378(1):11-21. doi:10.1056/nejmoa1706442.
9. Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;50(12):E344-E418. doi:10.1161/STR.0000000000000211.
10. Watanabe T, Tahara M, Todo S. The novel antioxidant edaravone: From bench to bedside. *Cardiovasc Ther* 2008;26(2):101-14. doi:10.1111/j.1527-3466.2008.00041.x.
11. Watanabe K, Tanaka M, Yuki S, Hirai M, Yamamoto Y. How is edaravone effective against acute ischemic stroke and amyotrophic lateral sclerosis? *J Clin Biochem Nutr* 2018;62(1):20-38. doi:10.3164/jcbn.17762.
12. Kikuchi K, Tancharoen S, Takeshige N, *et al*. The efficacy of edaravone (radicut), a free radical scavenger, for cardiovascular disease. *Int J Mol Sci* 2013;14(7):13909-30. doi:10.3390/ijms140713909.
13. Kikuchi K, Kawahara KI, Miyagi N, *et al*. Edaravone: A new therapeutic approach for the treatment of acute stroke. *Med Hypotheses* 2010;75(6):583-5. doi:10.1016/j.mehy.2010.07.038.
14. Wu S, Sena E, Egan K, Macleod M, Mead G. Edaravone improves functional and structural

outcomes in animal models of focal cerebral ischemia: A systematic review. *Int J Stroke* 2014;9(1):101-6. doi:10.1111/ijs.12163.
15. Feng S, Yang Q, Liu M, *et al*. Edaravone for acute ischaemic stroke. *Cochrane Database Syst Rev* Published online December 7, 2011. doi:10.1002/14651858.cd007230.pub2.
16. Yang J, Liu M, Zhou J, Zhang S, Lin S, Zhao H. Edaravone for acute intracerebral haemorrhage. *Cochrane Database Syst Rev* Published online February 16, 2011. doi:10.1002/14651858.cd007755.pub2
17. 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(4):907-917. doi:10.1111/jcpt.13392.
18. Fidalgo M, Ricardo Pires J, Viseu I, *et al*. Edaravone for acute ischemic stroke – Systematic review with meta-analysis. *Clin Neurol Neurosurg* 2022;219. doi:10.1016/j.clineuro.2022.107299.
19. Miyamoto S, Ogasawara K, Kuroda S, *et al*. Japan Stroke Society guideline 2021 for the treatment of stroke. *Int J Stroke* Published online 2022. doi:10.1177/17474930221090347.
20. Wahlgren N, Ahmed N, Dávalos A, *et al*. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275-82. doi:10.1016/s0140-6736(07)60149-4.
21. Degraba TJ, Hallenbeck JM, Pettigrew KD, Dutka AJ, Kelly BJ. Progression in acute stroke value of the initial NIH Stroke Scale Score on patient stratification in future trials. *Stroke* 1999;30:1208-12. doi:10.1161/01.str.30.6.1208.
22. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255-9. doi:10.1016/s0140-6736(00)02799-9.
23. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372. doi:10.1136/bmj.n71.
24. Enomoto M, Endo A, Yatsushige H, Fushimi K, Otomo Y. Clinical effects of early edaravone use in acute ischemic stroke patients treated by endovascular reperfusion therapy. *Stroke* 2019;50(3):652-8. doi:10.1161/STROKEAHA.118.023815.
25. Inatomi Y, Takita T, Yonehara T, *et al*. Efficacy of edaravone in cardioembolic stroke. *Int Med* 2006; 45(5):253-7. doi:10.2169/internal medicine.45.1423.
26. Ishibashi A, Yoshitake Y, Adachi H. Investigation of effect of edaravone on ischemic stroke. *Kurume Med J* 2013;60:1-5. doi:10.2739/kurumemedj.ms62009
27. Kaste M, Murayama S, Ford GA, Dippel DWJ, Walters MR, Tatlisumak T. Safety, tolerability and pharmacokinetics of mci-186 in patients with acute ischemic stroke: New formulation and dosing regimen. *Cerebrovasc Dis* 2013;36(3):196-204. doi:10.1159/000353680
28. 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(1-2):132-6. doi:10.1016/j.jns.2011.09.006.
29. Kono S, Deguchi K, Morimoto N, *et al*. Intravenous thrombolysis with neuroprotective therapy by edaravone for ischemic stroke patients older than 80 years of age. *J Stroke Cerebrovasc Dis* 2013;22(7):1175-83. doi:10.1016/j.jstrokecerebrovasdis.2013.02.010.
30. Lee XR, Xiang GL. Effects of edaravone, the free radical scavenger, on outcomes in acute cerebral infarction patients treated with ultra-early thrombolysis of recombinant tissue plasminogen activator. *Clin Neurol Neurosurg* 2018;167:157-61. doi:10.1016/j.clineuro.2018.02.026.
31. 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(1):73-9. doi:10.1159/000505776.
32. 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 (Tokyo)* 2015;55(3):241-7. doi:10.2176/nmc.ra.2014-0219
33. Otomo E, Tohgi H, Kogure K, *et al*. 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(3):222-9. doi:10.1159/000069318.
34. Sharma P, Sinha M, Shukla RK, Garg R, Verma R, Singh MK. A randomized controlled clinical trial to compare the safety and efficacy of edaravone in acute ischemic stroke. *Ann Indian Acad Neurol* 2011;14(2):103-6. doi:10.4103/0972-2327.82794.
35. Sun Z, Xu Q, Gao G, Zhao M, Sun C. Clinical observation in edaravone treatment for acute cerebral infarction. *Niger J Clin Pract* 2019;22(10):1324-7. doi:10.4103/njcp.njcp_367_18.
36. Toyoda K, Fujii K, Kamouchi M, *et al*. Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. *J Neurol Sci* 2004;221(1-2):11-7. doi:10.1016/j.jns.2004.03.002.
37. Wada T, Yasunaga H, Inokuchi R, *et al*. Effects of edaravone on early outcomes in acute ischemic stroke patients treated with recombinant tissue plasminogen activator. *J Neurol Sci* 2014;345(1):106-11. doi:10.1016/j.jns.2014.07.018.
38. Zheng J, Chen X. Edaravone offers neuroprotection for acute diabetic stroke patients. *Ir J Med Sci* 2016;185(4):819-24. doi:10.1007/s11845-015-1371-9.
39. 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(1):73-9. doi:10.1159/000505776.
40. Sun Z, Xu Q, Gao G, Zhao M, Sun C. Clinical observation in edaravone treatment for acute cerebral infarction. *Niger J Clin Pract* 2019;22(10):1324-7. doi:10.4103/njcp.njcp_367_18.
41. Lapchak PA. A critical assessment of edaravone acute ischemic stroke efficacy trials: Is edaravone an effective neuroprotective therapy? *Expert Opin*

Pharmacother 2010;11(10):1753-63. doi:10.1517/14656566.2010.493558.
42. Shibata H, Arai S, Izawa M, *et al*. Phase I clinical study of MCI-186 (Edaravone, 3-methyl-1-phenyl-2-pyrazolin-5-one) in healthy volunteers : Safety and pharmacokinetics of single and multiple administrations. *Jpn J Clin Pharmacol Ther* 1998;29(6):863-76.
43. Tsukamoto Y, Takizawa S, Takahashi W, *et al*. Effect of edaravone on the estimated glomerular filtration rate in patients with acute ischemic stroke and chronic kidney disease. *J Stroke Cerebrovasc Dis* 2011;20(2):111-6. doi:10.1016/j.jstrokecerebrovasdis.2009.11.008.
44. Yang HQ, Yin WJ, Liu K, Liu MC, Zuo XC. Renal safety evaluation of aspirin plus edaravone in patients with ischaemic stroke: a retrospective cohort study. *BMJ Open* 2022;12(4). doi:10.1136/bmjopen-2021-055469.
45. Kamouchi M, Sakai H, Kiyohara Y, Minematsu K, Hayashi K, Kitazono T. Acute kidney injury and edaravone in acute ischemic stroke: The fukuoka stroke registry. *J Stroke Cerebrovasc Dis* 2013;22(8). doi:10.1016/j.jstrokecerebrovasdis.2013.05.018.
46. Hirano M. Clinical evaluation of liver injury in patients with acute ischemic brain stroke treated with edaravone. *Hepatol Res* 2011;41(2):142-50. doi:10.1111/j.1872-034X.2010.00751.x.