Original Article
Efficacy of edaravone on coronary artery bypass patients with myocardial damage after ischemia and reperfusion: a meta analysis

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Abstract: Objectives: To assess the efficacy and safety of edaravone for myocardial damage during myocardial ischemia and reperfusion (I/R). Methods: We included randomized controlled trials that compared edaravone with placebo or no intervention in patients with acute myocardial infarction or undergoing coronary artery bypass. Two authors selected eligible trials, assessed trial quality and independently extracted the data. Results: Seven clinical trials were eventually included and analyzed in this study, involving 148 participants. Four trials were defined as waiting assessment. All of the three remaining trials compared edaravone and another treatment combined with other treatment alone, used the same dose of edaravone injections (60 mg per day) and course of treatment (14 days), evaluated the effect of edaravone at different times, applied different methods, reported adverse events, and showed no differences between the treatment group and the control group. When pooling all of the trials in one dataset, edaravone appeared to decrease the proportion of participant with marked myocardial damage during I/R as compared with the control group. The meta-analysis also revealed decreased CK-MB, cTnI and MDA, and increased content of SOD. Conclusions: Due to the moderate risk of bias and small sample, our observation of an effective treatment trend of edaravone for I/R requires future larger, high-quality trials to confirm.

Keywords: Myocardial, ischemia, reperfusion, edaraone
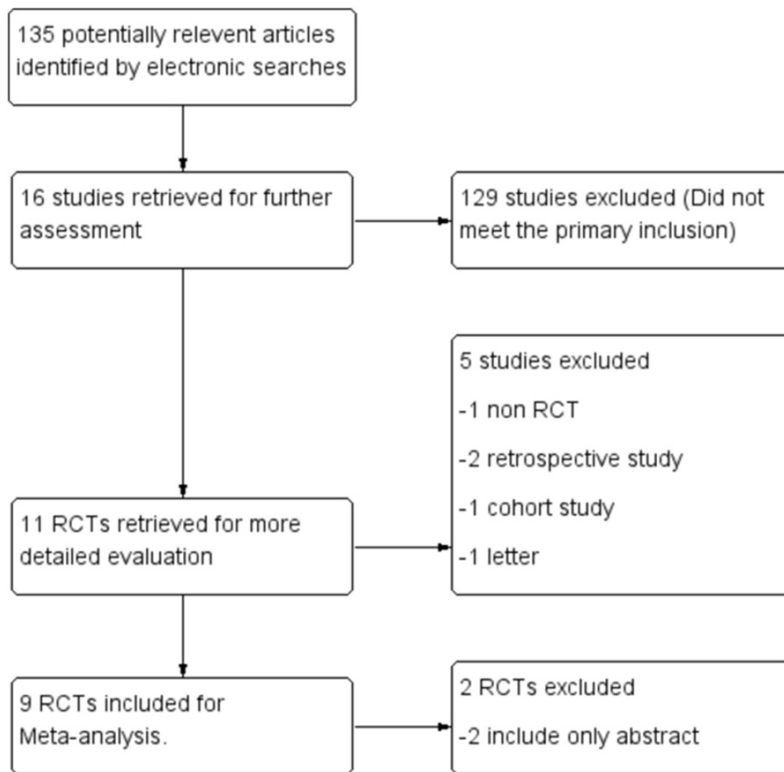
Introduction

Myocardial cell death caused by ischemia-reperfusion (I/R) is the main cause of morbidity and mortality in cardiovascular diseases [1]. Oxygen-derived free radicals play an important role in I/R [2]. Anti-oxidative free radicals therapeutic strategy for treating myocardial I/R has been reported in the past few decades [3], the outcomes of various clinical anti-oxidative free radicals therapeutic trials in the field of I/R injury have not proved effective for their low accessibility to tissue and quick clearance of body [4].

Interestingly, Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), with low molecular weight (174.20 KD), lipophilic and hydrosoluble ability for cell transmembrane [5], availability of scav-

enging toxic free radicals, affinity for lipids [6], is metabolized and excreted rapidly following conjugation to glucuronide or sulfate [5]. Edaravone functionally acts as a scavenger and antioxidant of ROS (reactive oxygen species: free radicals with unpaired electrons and oxidation ability) [5]. The antioxidant function is activated through transferring electrons from an edaravone anion to a peroxyl radical and thereby yields an edaravone radical and peroxyl anion, which breaks oxidation lipids [5], chain with elimination of a hydrogen atom and one electron that leads to enhancement of prostacyclin production. Prevention of the oxidative stress to the cell damage with inhibition of ROS [7] damage and eNOS expression [5].

Edaravone, essential for preventing myocardial ischemic-reperfusion (I/R) injury, has been rec-

135 potentially relevent articles identified by electronic searches

16 studies retrieved for further assessment

129 studies excluded (Did not meet the primary inclusion)

5 studies excluded

-1 non RCT

-2 retrospective study

-1 cohort study

-1 letter

11 RCTs retrieved for more detailed evaluation

9 RCTs included for Meta-analysis.

2 RCTs excluded

-2 include only abstract

Figure 1. The reasons for study inclusion/exclusion.

ognized as cardioprotective agent [8]. Japanese and India experimental studies have described its efficacy in acute ischemic stroke patients [9, 10]. Edaravone treatment prior to reperfusion averts ventricular tachyarrhythmias and cardiac function with I/R injuries [11]. This free radical scavenger for clinical is being widely used in coronary artery bypass surgery and urgent therapy for acute myocardial infarction in China, due to improved patient's outcomes. However, no meta-analysis has previously assessed the preventive effects of edaravone on myocardial (I/R) in China. The aim of this study was to investigate the effects in a sample of Chinese patients undergoing coronary artery bypass surgery and urgent therapy for acute myocardial infarction.

Materials and methods

Identification and eligibility of relevant studies

We exhaustively searched the databases of Embase, PubMed, CENTRAL, CBMdisc and CN-KI for relevant trials published, using the combinations of "edaravone", "MC186", "myocardial damage", "acute myocardial infarction", "coronary artery bypass", and "myocardial ischemia and reperfusion". There were no language re-

strictions. References of all trials were screened to identify additional relevant reports.

Data extraction

Two investigators reached a consensus on the eligibility for each study and independently extracted all required data, including first author, year of publication, CK-MB, TnI, MDA, SOD. Disagreement between the investigators was resolved by consulting a senior investigator.

Assessment of methodological quality

Two reviewers independently assessed the methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, incomplete outcome data addressed, free of selecting reports, free of other bias. We classified each quality component as "yes", "no", "unclear", with "Yes" representing a low risk of bias, "No" indicating a high risk of bias, and "unclear" suggesting an uncertain risk of bias (the Cochrane Handbook 5.0).

Statistical analysis

Meta-analysis was performed on all clinical trials comparing the efficacy of edaravone. In a case that continuous scales of measurement were used to assess the effects of treatment (24 h proteinuria or albuminuria, GFR, BP), the WMD and its 95% CI was used. Heterogeneity was determined with a chi-squared test on N-1 degrees of freedom [12]. Heterogeneity among the studies was also quantified using I^2 statistic, which provides values between 0% and 100% with greater degree of heterogeneity (I^2 = 0-25%: no heterogeneity; I^2 = 25-50%: moderate heterogeneity; I^2 = 50-75%: large heterogeneity; I^2 = 75-100%: extreme heterogeneity) [13]. A P value < 0.10 and I^2 > 50% indicated evidence of significant heterogeneity. The summary statistics was calculated by the fixed-effects model in the presence of heterogeneity; otherwise, the random-effects model was used.

Table 1. Principle characteristics of the studies included in the meta-analysis

First author	Journal	Study type	Sample size	
			edaravone	control
Hui Li	China Journal of Modern Medicine	Case control	10	10
Yijun Shi	Journal of Clinical Medicine in Pract ice	Case control	15	15
Qirong Xu	Practical Clinical Medicine,	Case control	15	15
Jingfeng Zhu	Journal of Jiangsu University	Case control	17	15
Jun Li	Chin J ECC	Case control	20	20
Zhifu Cai	Guangdong Medical Journal	Case control	30	30
Ya Shu	J Clin Anesthesiol	Case control	10	10
Li Wang	Modern Preventive Medicine	Case control	48	48
Xiaobo Wu	HAINAN MEDICAL JOURNAL	Case control	25	27

Table 2. Principle characteristics of the studies included in the meta-analysis

First author	Publication year	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free of selective reporting	Free of other bias
Hui Li	2012	Unclear	Unclear	Yes	MDA, SOD, cTnI	Yes	Unclear
Yijun Shi	2006	Unclear	Unclear	Yes	MDA, SOD, cTnI, CK-MB	Yes	Unclear
Qirong Xu	2007	Unclear	Unclear	Yes	CK-MB, MDA, SOD	Yes	Unclear
Jingfeng Zhu	2007	Unclear	Unclear	Yes	CK-MB, MDA	Yes	Unclear
Jun Li	2005	Unclear	Unclear	Yes	MDA, SOD, cTnI	Yes	Unclear
Zhifu Cai	2011	Unclear	Unclear	Yes	MDA, SOD, CK-MB	Yes	Unclear
Ya Shu	2013	Unclear	Unclear	Yes	MDA, SOD, cTnI, CK-MB	Yes	Unclear
Li Wang	2013	Unclear	Unclear	Yes	MDA, SOD, cTnI, CK-MB	Yes	Unclear
Xiaobo Wu	2011	Unclear	Unclear	Yes	MDA, CK-MB	Yes	Unclear

Yes: low risk of bias, No: high risk of bias, Unclear: risk of bias is unclear.

We used forest plots to describe an estimate of the overall results and variation between the results (heterogeneity) based on the individual studies that were included in the meta-analysis. Sensitivity analysis was employed to assess the validity of our pooled results.

Statistical analyses were performed using Rev-Man 5.0 (Cochrane Collaboration). All tests were two-sided with a threshold of $P < 0.05$.

Results

Study characteristics

Eight publications were finally considered eligible by referring to pr-defined inclusion criteria. The reasons for study inclusion/exclusion are graphically described in **Figure 1**.

The characteristics and quality of the studies are presented in **Tables 1**, **2** and **Figure 2**, respectively. Bias of the included studies are presented in **Figure 3**.

Effects of edaravone supplementation on CK-MB

Fixed effects model was used to calculate the pooled results. Overall, there was a significant difference in CKMB level of plasma (reference for myocardial injury) in the edaravone group, compared with the control group after artery open for 6 h and 24 h ($P < 0.05$).

Three trials reported the effects of edaravone on CK-MB within 6 h among patients undergoing coronary artery bypass surgery and urgent therapy for acute myocardial infarction (**Figure 4A**). Significant heterogeneity was found among these studies ($I^2 = 95\%$). The pooled results indicated that edaravone significantly reduced the level of circulating CK-MB (SMD = -4.16, 95% CI -7.43 to -0.90, $P = 0.01$; **Figure 4A**).

A total of four trials reported the effects of edaravone on CK-MB within 24 h in a group of patients who underwent coronary artery bypass surgery and urgent therapy for acute myocardial infarction (**Figure 4B**). Significant heteroge-

Figure 2. Quality of the included studies.
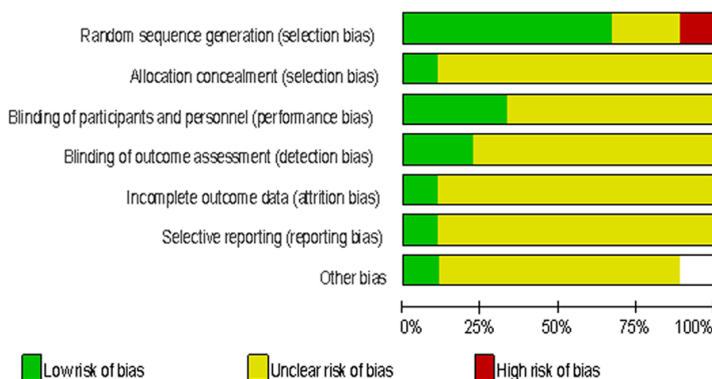
Figure 3. Bias of the included studies.

Effects of edaravone supplementation on cTnI

cTnI was significantly different from the control group in edaravone after opening artery for 6 h and 24 h ($P < 0.05$).

Three trials reported the effects of edaravone on cTnI within 6 h (**Table 3**). Significant heterogeneity was found among these studies ($I^2 = 65\%$). The pooled results showed that edaravone significantly decreased the level of circulating cTnI (SMD = -0.30, 95% CI -0.56 to -0.05, $P = 0.02$).

Four trials reported the effects of edaravone on cTnI within 24 h patients undergoing coronary artery bypass surgery and urgent therapy for acute myocardial infarction (**Table 3**). Significant heterogeneity was found among these study arms ($I^2 = 93\%$, $P = 0.0001$). The pooled results indicated that edaravone significantly decreased the level of circulating cTnI (SMD = -2.19, 95% CI -3.76 to -0.61, 0.007) in patients. Interestingly, Edaravone supplementation with a dose over 100 mg/day or for duration over 24 h seemed to associate with a greater reduction of circulating cTnI (**Table 3**).

Effects of edaravone supplementation on MDA

Following extracorporeal circulation and artery open for 6 h, and 24 h, the level of MDA differed significantly from the control group in edaravone ($P < 0.05$).

Four trials including 4 study arms reported the effects of edaravone on MDA within 6 h (**Table 3**). Significant heterogeneity was found among these study arms ($I^2 = 77\%$, $P = 0.004$). The pooled results showed that edaravone significantly reduced the level of circulating MDA (SMD = -1.73, 95% CI -2.66 to -0.80, $P = 0.0003$).

neity was found among these studies ($I^2 = 94\%$). A significant reduce in the level of circulating CK-MB was revealed in the pooled results (SMD = -2.73, 95% CI -4.29 to -1.16, $P = 0.0006$; **Figure 4B**).
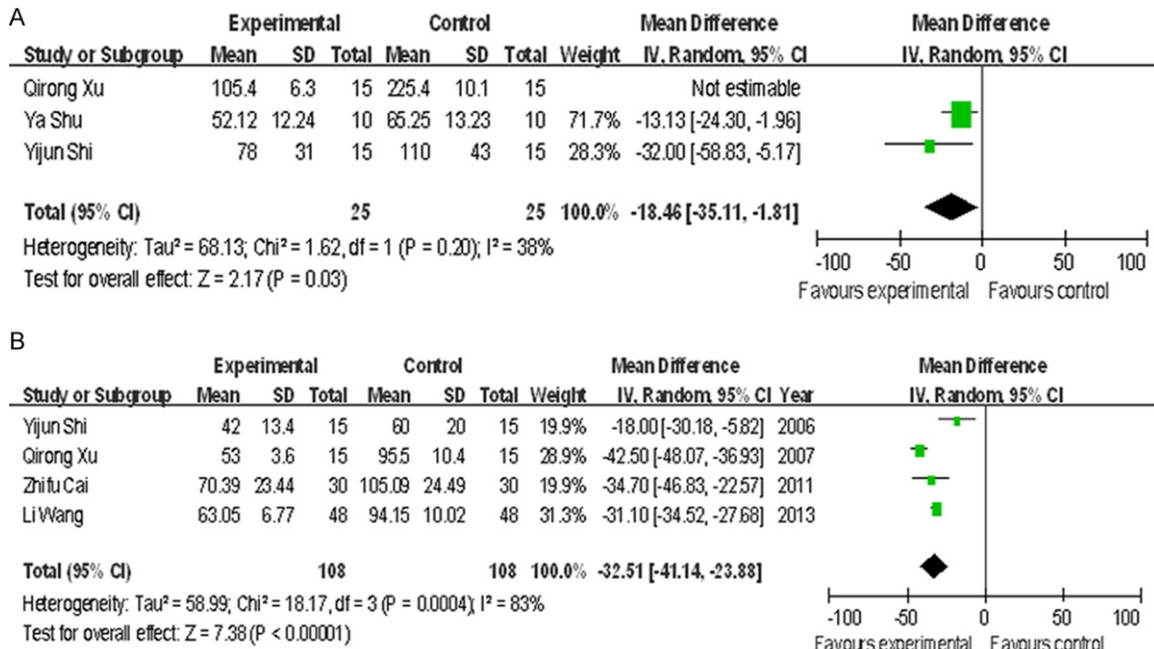
Figure 4. Levels of CK-MB at 6 h and 24 h.

Table 3. Levels of CK-MB, cTnI, MDA, SOD outcomes at 6 h and 24 h

Outcomes	No. of trails	No. of patients	MD (95% CI)	P
CK-MB 6 h	3	40/40	-4.16 [-7.43, -0.90]	0.01
24 h	4	108/108	-2.73 [-4.29, -1.16]	0.0006
cTnI 6 h	3	45/45	-0.30 [-0.56, -0.05]	0.02
24 h	4	93/93	-2.19 [-3.76, -0.61]	0.007
MDA 6 h	4	60/60	-1.73 [-2.66, -0.80]	0.003
24 h	8	173/175	-1.63 [-2.24, -1.02]	0.000
SOD 6 h	4	60/60	0.45 [-0.39, 1.29]	0.29
24 h	7	148/148	0.94 [0.69, 1.19]	0.000

Eight trials including 8 study arms reported the effects of edaravone on MDA within 24 h (**Table 3**). Significant heterogeneity was found among these study arms (I^2 = 82%, P < 0.00001). The pooled results revealed that edaravone significantly reduced the level of circulating MDA (SMD = -1.63, 95% CI -2.24 to -1.02, P < 0.00001).

Effects of edaravone supplementation on SOD

Following extracorporeal circulation and artery open for 6 h, and 24 h, the level of SOD significantly differed from the control group in edaravone (P < 0.05).

Three trials arms reported the effects of edaravone on SOD within 6 h in patients (**Table 3**).

Significant heterogeneity was found among these study arms (I^2 = 79%, P = 0.002). The pooled results indicated that edaravone significantly reduced the level of circulating SOD (SMD = 0.45, 95% CI -0.39 to 1.29, P = 0.29).

Seven trials arms reported the effects of edaravone on SOD within 24 h (**Table 3**). Significant heterogeneity was found among these study arms (I^2 = 81%, P < 0.0001). The pooled results indicated that edaravone significantly increased the level of circulating SOD (SMD = 0.94, 95% CI 0.69 to 1.19, P < 0.0001).

Sensitivity analysis

We performed sensitivity analyses to examine the stability of the results of this meta-analysis. The pooled ORs were not altered qualitatively when each study was excluded, suggesting our results are statistically reliable.

Publication bias

The funnel plot was employed to examine the publication bias (**Figure 3**). The shape of the funnel plots did not reveal asymmetry. In addi-

tion, Egger's test did not show any evidence of significant publication bias.

Discussion

Edaravone is an antioxidant treatment against I/R injury, with low accessibility to tissue and rapid clearance from the body [14]. It was first introduced into clinical use in Japan and proved effective for patients, all of whom had underwent cardiopulmonary by-pass operation [15]. Later, the clinical application was reported in India [16]. A wide use of this strategy is also seen in China for the treatment against I/R. Despite the increasing body of clinical literature describing edaravone as a cardioprotective agent in resistance to I/R in China, the efficacy has not been validated by means of a systematic review and meta analysis. To assess the effectiveness, safety and fidelity of the clinical treatment, we undertook a systematic review and meta analysis based on all currently available data.

Accumulating data have shown that ROS has a key role in myocardial damage during I/R and that they are associated with subsequent myocardial damage, and heart dysfunction [17]. ROS that is generated from initial reperfusion due to cell damage causes activation of tissue macrophages and recruitment of neutrophils for inflammatory response leading to cell death and cell injury [18]. Increased vascular oxidative stress or inflammation indicates the risk of cardiovascular events in patients with coronary artery disease [19]. Anti-oxidative stress or anti-inflammation has become an effective and promising method to reduce the myocardial damage during I/R [20]. Some radical scavengers and antioxidants including superoxide dismutase and vitamin E analog demonstrate effectiveness in the reduction of reperfusion-induced myocardial damage from oxidative stress and the inflammatory response [21].

Previous reports indicate that the antioxidant effects of edaravone may benefit the patients with cardiovascular outcomes; however, evidence of whether edaravone administration reduces ROS generation during the clinical course of I/R in humans is still very limited. We designed this systematic review and meta analysis on the basis of all randomized controlled trials in China to provide convincing evidence for the antioxidant effects. It is interestingly

that the antioxidant effects were enhanced and myocardial damage was strikingly decreased, accompanied with downregulation of cTnI and upregulation of MDA and SOD level. Edaravone is therefore a useful cardio-protective agent that contributes to nice clinical outcomes. As many meta-analyses, our study has several limitations, such as the length of observation time and small number of patients in each of the included trials. These limitations highlight that importance to further confirm the efficacy of edaravone in a study with a very large sample size.

In conclusion, edaravone is likely to be an effective cardio-protective agent and can be clinically used for I/R injury in patients with acute myocardial infarction and coronary artery bypass grafting.

Acknowledgements

Disclosure of conflict of interest

None.

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