Meta-analysis of the Efficacy and Safety of Edaravone Dexborneol in the Treatment of Cerebral Infarction

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Abstract. The purpose is to evaluate the efficacy and safety of edaravone dexborneol in treating cerebral infarction. Methods: Computer searches were conducted on databases such as PubMed, Cochrane Library, and Web of Science to identify randomized controlled trials of edaravone dexborneol in treating cerebral infarction. Meta-analysis was performed by Review Manager 5.4.1 software on eligible studies. Results: A total of 10 studies meeting the inclusion criteria were included, with a total of 3,324 patients. The Meta-analysis showed that compared to the control group, edaravone dexborneol significantly improved total effective rate, enhanced excellent functional outcomes, and reduced IL-6 levels, with statistically significant differences; however, there were no statistically significant differences in neurological function improvement compared to the control group; in terms of reducing adverse reactions, the control group had a more favorable outcome than edaravone dexborneol, with statistically significant differences. Conclusion: Edaravone dexborneol can significantly improve clinical outcomes in treating cerebral infarction, but may increase the incidence of adverse reactions. Therefore, it is necessary to select appropriate treatment regimens based on clinical circumstances to achieve optimal clinical outcomes.

Keywords: Edaravone Dexborneol; Cerebral Infarction; Meta-analysis.

1. Introduction

Cerebral infarction is a common cardiovascular disease characterized by rapid onset, high recurrence rate, and high mortality, posing a severe threat to patients physical and mental health. Epidemiological studies show that cerebral infarction predominantly affects middle-aged and elderly populations, with its incidence increasing in recent years and showing a trend toward younger age groups. Cerebral infarction mainly results from thrombosis, cerebral artery atherosclerosis, foreign bodies entering the brain, or carotid arteries leading to vessel stenosis or obstruction, causing blood flow interruption or a sudden decrease in blood flow to the brain, resulting in ischemia and hypoxia of brain tissue, which leads to brain tissue necrosis and neurological deficits. After ischemia and hypoxia-induced necrosis of brain tissue, a large amount of harmful free radicals is produced, oxidizing brain cells and causing neuronal death, increased cell membrane permeability, and cerebral edema. In 2020, edaravone dexborneol, a Class I innovative drug newly launched in China, was developed by adding edaravone to dexborneol at a ratio of 4:1. It has a synergistic effect in scavenging free radicals and inhibiting inflammatory-related proteins, combining neuroprotection and functional recovery mechanisms, significantly enhancing clinical efficacy. An increasing number of studies have reported on the clinical research of edaravone dexborneol for treating cerebral infarction. This study systematically evaluates the efficacy and safety of edaravone dexborneol in treating cerebral infarction through Meta-analysis, aiming to provide evidence-based medicine for related clinical diagnosis and treatmentevidence.

2. Data and Methods

1.1 The study was a randomized controlled trial in English.

1.2 The subjects were diagnosed with cerebral infarction according to the internationally recognized diagnostic criteria, and confirmed by CT or MRI. There was no restriction on gender and age.

1.3 Outcome indicators: 1) Total effective rate. 2) Neurological function improvement (National Institutes of Health stroke scale (NIHSS)score on 0-1 points after 14 days). 3) Excellent functional outcome (modified Rankin scale (mRS) score on0-1 points after 90 days). 4) IL-6 (Interleukin-6). 5) Adverse reaction.

2 Exclusion criteria

1) No outcome indicators mentioned. 2) Republished literature. 3) Animal experiments. 4) Pharmacological experiments. 5) Studies with serious data errors. 6) Studies where key data cannot be extracted or converted.

3 Literature retrieval strategy

The databases of Web of Science, PubMed and Cochrane Library were searched to review the relevant literature of edaravone dexborneol in the treatment of cerebral infarction. The search time was from database establishment to November 2024. The search terms included "cerebral Infarction", "Ischemic Stroke", and "edaravone dexborneol".

4 Literature screening

The retrieval, screening and data extraction of the literature were independently conducted by two researchers. In case of disputes during this process, two researchers would discuss together or a third researcher would be invited to negotiate and solve the problems.

5 Quality evaluation

The included studies were assessed for bias risk by two evaluators using the Cochrane Manuals bias risk assessment tool, which includes seven items: randomization method, allocation concealment, participant blinding, outcome evaluation blinding, data completeness, selective reporting, and other biases. Each bias risk is categorized into three levels: "low risk" indicates low bias; "unclear" indicates unclear bias; "high risk" indicates high bias. A risk bias diagram was drawn using Review Manager 5.4.1.

6 Statistical analyses

This study used Review Manager 5.4.1 software for Meta analysis. I^2 was Used to assess the heterogeneity of the study results, When the proportion of I^2 was less than 50%, a fixed effects model should be used; otherwise, a random effects model should be employed. The mean difference (MD) serves as the effect measure for continuous data, while the relative risk (RR) was used for binary count data. Effects were presented with a 95% confidence interval (CI), and $P < 0.05$ indicates statistically significant differences.

3. Result

3.1 Literature Search Result

A total of 142 relevant articles were preliminarily retrieved, including PubMed 54, Cochrane Library 42 and Web of science 46. After preliminary screening, 36 articles remained. After reading the full text and final screening, 8 articles were finally included.

3.2 Basic Characteristics of Inclusion in Research

A total of 3,324 patients were included in the 10 studies, including 1,672 in the trial group and 1,652 in the control group. The basic characteristics of the included studies are shown in Table 1.

3.3 Evaluation of Included Research Quality

The bias risk assessment tool from the Cochrane manual was used to evaluate the bias risk of the included studies. Two studies used random number table method, six studies used computer-generated randomization, six studies employed concealed allocation, and six studies were double-

blind. All study data were complete, with no selective reporting of results identified. The results of the bias risk assessment are shown in Figure 1.

Table 1. Basic characteristics included in the study

Included studies	Sample size (cases)		Male/female (example)		Age (years)		Intervention measures		Course of treatment (d)	Outcome indicators
	T	C	T	C	T	C	T	C		
Fu, 2024[1]	450	464	309/141	299/165	56-69.8	57.1-71.4	36mg edaravone dexborneol was administered sublingually twice a day	conventional therapy	14	2)3)5)
Li, 2024[2]	100	100	45/55	51/49	66.44±5.03	68.31±5.32	On the basis of the control group, 37.5mg edaravone dexborneol was given intravenously twice a day	On the basis of conventional treatment, 25mg diphenylphenol was given intravenously twice a day	14	1)
Mi, 2024[3]	40	40	25/15	23/17	61.9±8.9	62.5±8.7	On the basis of terolafen treatment, 37.5mg edaravone dexborneol was administered intravenously twice a day	tirofiban	14	4)5)
Xu, 2024[4]	51	42	37/14	28/14	67.88±13.168	69.24±11.941	On the basis of standardized treatment, 37.5mg edaravone dexborneol was given intravenously twice a day	Standardized treatment	14	4)5)
Zhang, 2023[5]	72	56	-	-	-	-	On the basis of conventional treatment, 15ml edaravone dexborneol was administered twice daily	conventional therapy	14	1)
Hu, 2023[6]	69	73	45/24	44/29	65.8±11.0	66.6±12.7	On the basis of standardized treatment, 37.5mg edaravone dexborneol was given intravenously twice a day	Standardized treatment	10-14	3)4)
Xu, 2021[7]	599	595	404/195	407/188	55.38-68.96	55.72-70.12	Gave 37.5mg edaravone dexborneol injection twice a day	edaravone injection was given at 30mg per dose, twice daily	14	2)3)
Xu (low-dose),2019[8]	97	94	67/30	65/29	58.13±8.46	59.71±8.33	Gave 12.5mg edaravone dexborneol injection twice a day	edaravone injection was given at 30mg per dose, twice daily	14	2)3)5)
Xu (medium-dose), 2019[8]	98	94	65/33	65/29	59.11±8.95	59.71±8.33	Gave 37.5mg edaravone dexborneol injection, 2 times a day	edaravone injection was given at 30mg per dose, twice daily	14	2)3)5)
Xu(high-dose), 2019[8]	96	94	64/32	65/29	59.55±9.53	59.71±8.33	Gave 62.5mg edaravone dexborneol injection, 3 times a day	edaravone injection was given at 30mg per dose, twice daily	14	2)3)5)

Note: T: test group; C: control group; --: not reported; 1) total effective rate; 2) neurological function improvement; 3) excellent functional outcome; 4) IL-6; 5) adverse reaction

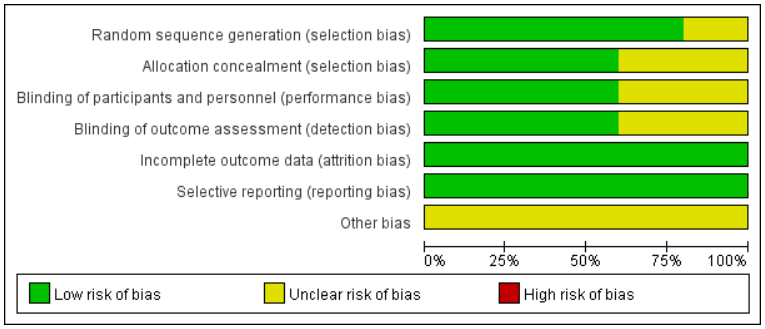

Figure 1. Bar chart of bias risk

3.4 Meta-analysis Result

1 total effective rate 2 studies reported total effective rate, and the included studies without heterogeneity (P = 0.56, I^2=0%), so a fixed effect model was used. The results showed that the total effective rate of edaravone dexborneol treatment for cerebral infarction was more advantageous than that of the control group, with a statistically significant difference (RR=1.33,95%CI[1.17,1.51], P<0.00001), as shown in Figure 2.

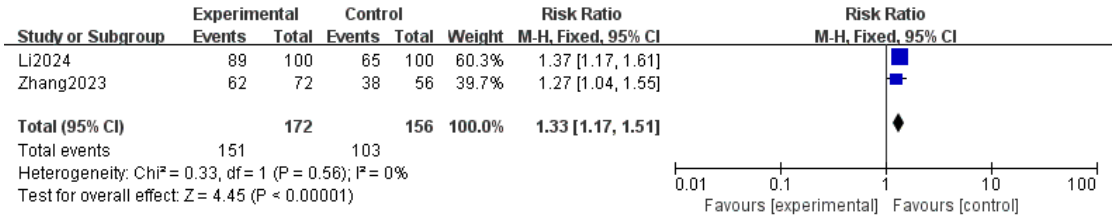

Figure 2. Meta-analysis forest plot of total effective rate

2 neurological function improvement There were 5 studies reported neurological function improvement, and the included studies without heterogeneity (P=0.59, I^2=0%), so the fixed effect model was used. The results showed that there was no statistically significant difference between edaravone dexborneol and the control group in terms of neurological function improvement (RR=0.89,95% CI[0.77,1.04], P=0.15), see Figure 3.

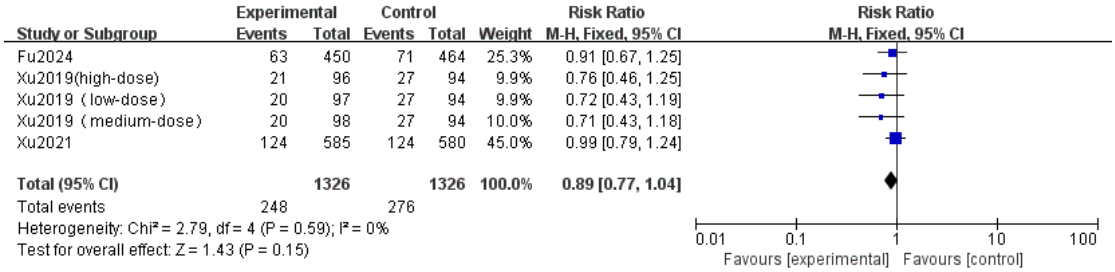

Figure 3. Meta-analysis forest plot of neurological function improvement

3 excellent functional outcome 3 studies reported excellent functional outcome, and the included studies without heterogeneity (P=0.72, I^2=0%), so the fixed effect model was used, and the result showed that in terms of improving excellent functional outcomes, edaravone dexborneol had a greater advantage compared with the control group, with a statistically significant difference (RR=1.14,95%CI[1.08,1.21], P<0.0001), as shown in Figure 4.

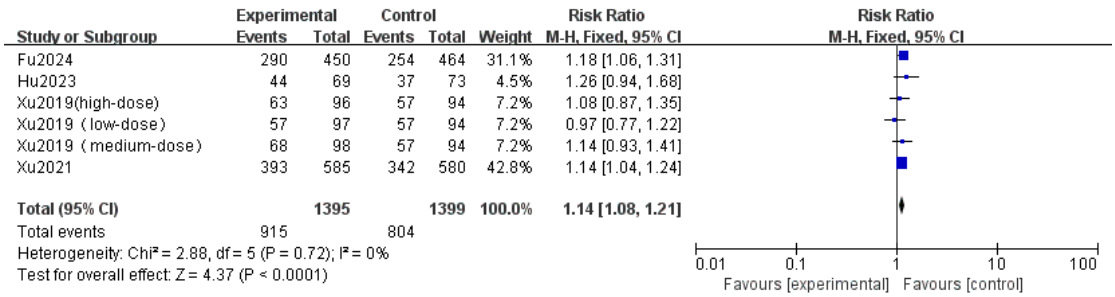

Figure 4. Meta-analysis forest plot of excellent functional outcome

4 IL-6 3 studies reported IL-6, and the included studies without heterogeneity (P = 0.52, I^2= 0%), so the fixed effect model was used. The result showed that in reducing IL-6 levels, edaravone

dexborneol was more advantageous than the control group, and the difference was statistically significant (MD= -3.14,95%CI [-3.47, -2.82], P <0.00001), as shown in Figure 5.

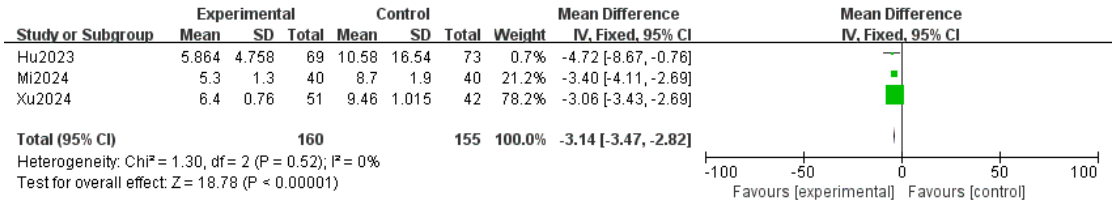

Figure 5. Meta-analysis forest plot of IL-6

5 adverse reaction A total of 6 studies were reported adverse reaction without heterogeneity (P=0.93, I^2=0%), so the fixed effect model was used, and the result showed that the incidence of adverse reaction in the control group was lower than that in edaravone dexborneol, with a statistically significant difference (RR=1.37,95%CI[1.04,1.81], P=0.02), as shown in Figure 6.

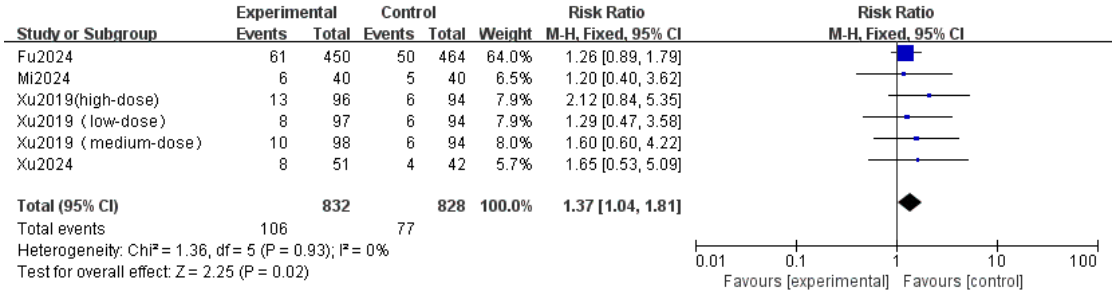

Figure 6. Meta-analysis forest plot of adverse reaction

4. Discuss

Although there was no significant difference in neurological function improvement (NIHSS score 0-1) between edaravone dexborneol and the control group after 14 days of treatment, at 90 days, the edaravone dexborneol group showed a statistically significant advantage in excellent functional outcome (mRS score 0-1) compared to the control group. Additionally, edaravone dexborneol significantly increased the total effective rate of patients compared to the control group. This indicates that edaravone dexborneol can significantly enhance clinical outcomes when used for treating cerebral infarction. However, the incidence of adverse reactions in the control group was lower than that in the edaravone dexborneol group, suggesting that while edaravone dexborneol improves clinical outcomes, it may also increase the incidence of adverse reactions. Therefore, appropriate medication regimens should be selected based on clinical circumstances to achieve optimal clinical outcomes.

This study also has some limitations. Some of the included RCTs lack allocation concealment and are not completely double-blind. The patients included in the trials have differences in age limit, disease duration, routine drug use, and the sample size of the included studies is generally small, which may lead to bias.

In summary, edaravone dexborneol can significantly improve clinical outcomes in the treatment of cerebral infarction, but may increase the incidence of adverse reactions. It is necessary to select appropriate medication regimens based on clinical circumstances to achieve optimal clinical efficacy. The results of this study can provide evidence-based medical support for the use of edaravone dexborneol in treating cerebral infarction.

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