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Observation on the Efficacy of Edaravone Dexborneol in the Treatment of Large-area Cerebral Infarction

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Abstract: *Objective:* To explore the efficacy and safety of edaravone dexborneol in the treatment of patients with large-area cerebral infarction by comparing the GCS score, mRS score, NIHSS score, BI score, and hs-CRP results before and after treatment, as well as the mRS score, mortality rate, length of hospital stay, and adverse reactions after 90 days of treatment between the two groups. *Methods:* A total of 102 patients with acute large-area cerebral infarction who were hospitalized in the neurology department of Shaanxi Provincial People's Hospital from October 2020 to December 2021 were selected as the research subjects. All patients were randomly divided into an experimental group and a control group, with 51 patients in each group. The control group received conventional treatment, thrombolytic therapy, and endovascular interventional therapy, while the experimental group received additional edaravone dexborneol treatment for 14 days based on the above treatment methods. The GCS score, mRS score, NIHSS score, BI score, and hs-CRP results before and after treatment, as well as the mRS score, mortality rate, length of hospital stay, and adverse reactions after 90 days of treatment, were collected and statistically analyzed using SPSS 25.0. *Results:* The two groups were comparable at baseline, with no significant differences in demographics, laboratory parameters, stroke subtype (TOAST), neurological deficit (NIHSS), functional status (mRS, BI), consciousness (GCS), or inflammation (hs-CRP) (all $P > 0.05$). After 14 days of treatment, the experimental group demonstrated a significantly higher overall response rate (78.4% vs. 52.9%, $P = 0.007$), greater reduction in NIHSS score ($P = 0.043$) and greater increase in BI score ($P = 0.017$), while changes in GCS and mRS remained similar between groups ($P > 0.05$). Moreover, the experimental group achieved larger pre-to-post treatment improvements in NIHSS ($P = 0.032$) and BI ($P = 0.013$), but not in GCS or mRS ($P > 0.05$). Inflammatory marker hs-CRP decreased more markedly in the experimental group at day 14 and showed a greater change from baseline (both $P < 0.001$). By day 90, the experimental group exhibited lower mRS scores and greater mRS improvement than controls ($P = 0.011$ and $P = 0.038$, respectively), without differences in mortality ($P > 0.05$). Finally, there were no significant differences between groups in hospital length of stay or adverse event rates ($P > 0.05$), indicating both regimens were similarly safe and well tolerated. *Conclusion:* Edaravone dexborneol can effectively improve neurological deficits in patients with large-area cerebral infarction, improve patients' quality of life, and has good safety. Edaravone dexborneol can improve inflammatory indicators in patients with

large-area cerebral infarction, which is one of the mechanisms of edaravone dexborneol in the treatment of large-area cerebral infarction. Edaravone dexborneol can improve the short-term prognosis of patients with large-area cerebral infarction.
Keywords: Edaravone dexborneol; Large-area cerebral infarction; mRS Score; NIHSS score; hs-CRP; Prognosis

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1. Introduction

Currently, with the continuous growth of China's population and the increase in the elderly population, the prevalence and mortality of cerebrovascular diseases are also gradually rising. Cerebrovascular disease is the second leading cause of death globally and the leading cause of death in China [1,2]. Acute cerebral infarction is the most common type of stroke, accounting for 69.9–70.8% of strokes in China [3,4]. Large hemispheric infarction (LHI) is the most critical and clinically severe form, with very high mortality and disability rates, poor prognosis, and severe psychological and economic impacts on patients and their families [5]. Typically, large artery occlusions such as the middle cerebral artery, internal carotid artery, and basilar artery can cause large-area cerebral infarction [6]. Clinical manifestations include conjugate deviation, hemiplegia, aphasia, and altered levels of consciousness such as lethargy and coma. Most patients develop cerebral edema, and intracranial pressure imbalances can cause brain tissue shifts leading to herniation and potentially life-threatening changes in vital signs. The incidence of LHI is 10–20 per 100,000 people per year, accounting for 10% of supratentorial ischemic strokes [7]. Despite active medical treatment for large-area cerebral infarction, the mortality rate remains close to 80%, and approximately 66.7% of patients are left with disabilities, severely affecting people's health and quality of life [6,8–10].

The focal lesion of cerebral infarction consists of the core infarct zone and the surrounding ischemic penumbra. In the core infarct zone, nerve cells have undergone apoptosis due to insufficient energy supply and inflammatory damage, and there is no therapeutic value. However, there is still an opportunity to save the nerve cells in the ischemic penumbra. If blood perfusion can be provided in a timely manner and inflammation and oxidative stress reactions caused by ischemia can be reduced, nerve cells will receive a timely oxygen supply, allowing mitochondria to continue producing energy and greatly improving their survival rate. As a result, the total area of cerebral infarction will be reduced. Therefore, the main clinical goal in treating cerebral infarction is to minimize nerve cell damage in the ischemic penumbra. Currently, reperfusion therapies, including intravenous thrombolysis and endovascular interventional therapy (such as thrombus aspiration and mechanical thrombectomy), can significantly improve the survival rate of neurons in the ischemic penumbra, thereby reducing infarct size and improving functional prognosis. With technological advancements and innovations, reperfusion therapy methods are constantly evolving. However, both intravenous thrombolysis and endovascular interventional therapy have strict indications and contraindications, limiting their application if treatment conditions are not met. In contrast, neuroprotective therapies have not made significant progress in recent years. As one of the important methods to save the ischemic penumbra, it is necessary to focus on the research of neuroprotective drugs.

Edaravone, as an antioxidant drug, has been proven to reduce oxidative stress reactions caused by ischemia by scavenging free radicals, peroxyl radicals, and superoxide radicals, inhibiting delayed neuronal death and improving the prognosis of cerebral infarction [11,12]. Both Chinese and Japanese stroke guidelines recommend the use of edaravone for the treatment of acute cerebral infarction [13, 14]. However, edaravone as a single neuroprotective target is far from sufficient, and more antioxidant and anti-inflammatory targets are needed to improve the oxidative stress state. Recent

studies have found that dexborneol, a naturally occurring organic molecule, can inhibit the expression of inflammatory factors such as TNF-α and IL-1β after cerebral ischemia, blocking the damage of inflammation to nerve cells [15,16]. The synergistic effect of these two components can exert better neuroprotective effects. Current research has found that compared to the control group, the edaravone dexborneol group can better reduce the NIHSS score ($P < 0.05$) and improve the BI score ($P < 0.05$) of patients with cerebral infarction, resulting in a good functional prognosis [17]. It can also reduce various inflammatory indicators, effectively alleviate the oxidative stress state of patients with cerebral infarction, and has good safety [18].

However, there is currently limited clinical data on the use of edaravone dexborneol for the treatment of large-area cerebral infarction. Therefore, this study intends to explore the efficacy and safety of edaravone dexborneol in the treatment of large-area cerebral infarction, providing more options for clinical practice.

2. Materials and methods

2.1. Subjects

Patients with large-area cerebral infarction who were hospitalized in the neurology department of Shaanxi Provincial People's Hospital from September 2021 to December 2022 were selected as the study subjects. All enrolled patients met the classification criteria for large-area cerebral infarction according to the Adama method: infarction diameter ≥ 3 cm, involving more than two anatomical sites. Finally, 102 patients were included and randomly divided into a control group ($n = 51$) and an experimental group ($n = 51$) using a random number table method. This study was reviewed and approved by the Ethics Management Committee of Shaanxi Provincial People's Hospital.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Age between 18 and 80 years old; (2) Onset within 48 hours; (3) CT or MRI examination indicating diagnosis criteria for large-area cerebral infarction; (4) History of cerebrovascular disease without sequelae, and mRS ≤ 1 before stroke onset; (5) Patient or family members willing to participate in this study with verbal consent.

Exclusion criteria: (1) Age ≤ 18 or ≥ 80 years old; (2) Severe organ dysfunction such as heart, liver, kidney, or cancer with a short estimated survival time; (3) Allergy to any component of the study medication; (4) Refusal to participate in this study; (5) Pregnant women; (6) Transfer to neurosurgical treatment during the course of the study.

3. Research methods

3.1. Treatment methods

Both groups of patients with large-area cerebral infarction received conventional treatment, intravenous thrombolysis, and endovascular therapy. The experimental group received additional intravenous infusion of edaravone dexborneol on the basis of the above treatments, with 15 mL administered twice a day, completed within 30 minutes, for a continuous period of 14 days.

3.2. Collection of general clinical data

Detailed general information was collected for all enrolled patients in both the experimental and control groups, including name, gender, age, phone number, past medical history, Body Mass Index (BMI), and personal history. Diagnostic criteria for cerebrovascular disease risk factors are as follows: (1) Hypertension [19]: Meets the diagnostic

criteria for hypertension revised in 2018. (2) Diabetes [20]: Meets the diagnostic criteria in the new guidelines for diabetes in 2019. (3) Heart disease: Includes coronary atherosclerotic heart disease, arrhythmia, and other conditions. Diagnosis is made by a cardiologist based on tests such as myocardial enzymes, electrocardiogram, echocardiography, coronary CT angiography, and cardiac angiography. (4) Hyperlipidemia: Meets the diagnostic criteria in the "Guidelines for the Prevention and Treatment of Dyslipidemia in Chinese Adults 2016" [21], or has been previously diagnosed with hyperlipidemia.

3.3. Collection of laboratory indicators

The following laboratory tests were performed on an empty stomach in the early morning of the second day after admission: white blood cells, urine routine, liver and kidney function, electrolytes, random blood glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glycated hemoglobin, and homocysteine (HCY). Changes in liver and kidney function, blood routine, and urine routine were monitored during treatment. hs-CRP (Hypersensitive C-reactive protein) was collected on the day of admission and after 14 days of inpatient treatment. All experimental data were provided by the clinical laboratory and radiology department of Shaanxi Provincial People's Hospital.

3.4. Imaging examination

Within 48 hours of admission, cranial CT scan and/or MRI examination were completed. The cranial magnetic resonance imaging instrument was a Philips Intera Achieva 1.5 T superconducting magnetic resonance scanner, and T1WI, T2WI, FLAIR, DWI, and MRA examinations were performed.

3.5. Stroke scale scores

On admission, patients were assessed using the GCS, NIHSS, mRS, and BI scores. These assessments were repeated on the 14th day of the patient's hospital stay. A follow-up assessment was conducted on the 90th day of inpatient treatment, including the mRS score and mortality rate to evaluate the patient's prognosis. Follow-up methods could include outpatient visits, inpatient revisits, or telephone interviews. The GCS, NIHSS, mRS, and BI scoring scales are provided in the appendix.

3.6. Clinical efficacy evaluation

NIHSS scores were collected for both groups of patients before and after treatment. The neurological improvement rate was calculated using the formula: (pretreatment total score - post-treatment total score) / pretreatment total score. Based on the improvement rate, patients were classified into the following five categories: (1) Improvement rates between 91–100% were considered as basic recovery; (2) Improvement rates between 46–90% were considered as significant improvement; (3) Improvement rates between 18–45% were considered as improvement; (4) Improvement rates below 17% were considered as ineffective; (5) An increase in the improvement rate by more than 18% or death was considered as deterioration. Generally, we consider basic recovery, significant improvement, and improvement as effective. The effective rate was calculated as: (basic recovery + significant improvement + improvement) / (basic recovery + significant improvement + improvement + ineffective + deterioration).

3.7. Observation indicators for adverse drug reactions

During the treatment process, liver and kidney function, electrolytes, and blood routine were monitored, and patients were observed for allergic reactions such as rash, dyspnea, and other adverse reactions.

3.8. Statistical Analysis

3.8.1. Estimation of sample size

A preliminary experiment was conducted before the start of the study, which showed that the effective rate was 76% in the experimental group and 50% in the control group. Based on $\alpha = 0.05$ and $\beta = 0.20$ (two-sided test), using PASS 15.0 software, it was calculated that a minimum sample size of 51 cases was required for each group. Details are shown in **Table 1**.

Table 1. Sample size estimation table

Target	Actual						Diff	
Power	Power*	N1	N2	N	P1	P2	D1	Alpha
0.8	0.81	51	51	102	0.76	0.50	0.26	0.05

3.8.2. Data processing method

In this study, SPSS 25.0 statistical software was used for statistical analysis of all data. Clinical efficacy, past medical history, personal history, and other qualitative data were expressed as frequency/percentage, and the chi-square test was used to compare the results between the two groups. Scores, laboratory data, age, and other quantitative data were analyzed as follows: quantitative data conforming to a normal distribution were expressed as mean ± standard deviation (SD). A paired-sample *t*-test was used before and after treatment in each group, and an independent-sample t-test was used for comparison between the two groups. Quantitative data that did not conform to a normal distribution were expressed as median and interquartile range. A paired Wilcoxon signed-rank test was used before and after treatment in each group, and a Wilcoxon rank-sum test was used for comparison between the two groups. All statistical analyses were performed at a significance level of $\alpha = 0.05$. Graphs were created using GraphPad Prism 9.3 software.

4. Results

4.1. Comparison of basic information

4.1.1. Comparison of general information between the two groups

In the control group, there were 25 males and 26 females, with an average age of (69.50 ± 16.32) years old, an average BMI of (22.22 ± 3.01) kg/m^2. The average systolic blood pressure at admission was (141.50 ± 22.67) mmHg, and diastolic blood pressure was (83.61 ± 16.36) mmHg. The median pre-stroke mRS was 0. There were 32 patients with hypertension, 16 with diabetes, 13 with coronary heart disease, 15 with hyperlipidemia, 13 with atrial fibrillation, 9 with stroke history, 8 smokers, and 3 alcohol consumers. A total of 10 patients underwent intravenous thrombolysis or endovascular interventional therapy. There were 23 patients with left cerebral hemispheric infarction and 28 with right cerebral hemispheric infarction. In the experimental group, there were 27 males and 24 females, with an average age of (68.40 ± 14.61) years and an average BMI of (23.01 ± 3.86) kg/m^2. The average systolic blood pressure at admission

was (146.51 ± 18.17) mmHg, and diastolic blood pressure was (81.78 ± 14.27) mmHg. The median pre-stroke mRS was 0. There were 37 patients with hypertension, 15 with diabetes, 15 with coronary heart disease, 17 with hyperlipidemia, 9 with atrial fibrillation, 14 with stroke history, 9 smokers, and 3 alcohol consumers. A total of 7 patients underwent intravenous thrombolysis or endovascular interventional therapy. There were 20 patients with left cerebral hemispheric infarction and 31 with right cerebral hemispheric infarction. There were no statistically significant differences between the two groups in baseline data such as age, gender, past medical history, personal history, BMI, blood pressure at admission, pre-stroke mRS score, and TOAST classification (all $P > 0.05$). Details are shown in **Table 2** and **Table 3**.

Table 2. Comparison of general information between the two groups ($n = 102$)

Item	Control group ($n = 51$)	Experimental group ($n = 51$)	□²/t/t'/Z value	*P* value
Age (years)	69.50 ± 16.32	68.40 ± 14.61	0.32	0.753
Gender (male/female)	25/26	27/24	0.16	0.692
Hypertension (cases, %)	32 (62.75%)	37 (72.55%)	1.12	0.290
Diabetes (cases, %)	16 (31.37%)	15 (29.41%)	0.05	0.830
Coronary heart disease (cases, %)	13 (25.49%)	15 (29.41%)	0.20	0.657
Hyperlipidemia (cases, %)	15 (29.41)	17 (33.33%)	0.18	0.670
Atrial fibrillation (cases, %)	13 (25.49%)	9 (17.65%)	0.93	0.336
Stroke (cases, %)	9 (17.65%)	14 (27.45%)	1.40	0.236
Smoking history (cases, %)	8 (15.69%)	9 (17.65%)	0.07	0.790
Drinking history (cases, %)	3 (5.88%)	2 (3.92%)	*	1.000
BMI (kg/m^2)	22.22 ± 3.01	23.01 ± 3.86	-1.04	0.301
Systolic blood pressure at admission (mmHg)	141.50 ± 22.67	146.51 ± 18.17	-1.10	0.273
Diastolic blood pressure at admission (mmHg)	83.61 ± 16.36	81.78 ± 14.27	0.53	0.597
mRS score before stroke	0 (0.00)	0 (0.00)	-1.20	0.230
Intravenous thrombolysis or interventional therapy	10 (19.61%)	7 (13.73%)	0.64	0.425
Side of cerebral infarction (left/right)	23/28	20/31	0.36	0.547

Note: * represents the use of Fisher's test.

Table 3. Comparison of TOAST classification between the two groups

TOAST classification	Control group ($n = 51$)	Experimental group ($n = 51$)	c^2 value	*P* value
Large artery atherosclerosis type (cases, %)	28 (54.90%)	38 (74.51%)	4.72	0.061
Cardioembolic stroke type (cases, %)	22 (43.14%)	13 (25.49%)		
Small artery occlusion (cases, %)	0 (0)	0 (0)		
Stroke of other determined etiology (cases, %)	1 (1.96%)	0 (0)		
Stroke of undetermined etiology (cases, %)	0 (0)	0 (0)		

4.2. Comparison of laboratory indices between the two groups

There were no statistically significant differences in laboratory results for white blood cells, total protein, albumin, LDL-C, TC, HDL-C, TG, glycated hemoglobin, random blood glucose, and HCY between the two groups at admission ($P > 0.05$). Details are shown in **Table 4**.

Table 4. Comparison of laboratory test results between the two groups

Item	Control group	Experimental group	*t*/Z value	*P* value
White blood cells (10^9/L)	9.05 ± 2.94	8.07 ± 2.61	0.79	0.431
Total protein (g/L)	64.40 (5.52)	64.60 (8.30)	-0.68	0.632
Albumin (g/L)	34.55 (6.35)	35.1 (7.75)	-1.72	0.085
TC (mmol/L)	3.54 (1.25)	4.08 (1.32)	-1.54	0.125
HDL-C (mmol/L)	0.97 (0.38)	1.06 (0.32)	-0.88	0.378
LDL-C (mmol/L)	2.12 (1.15)	2.54 (1.74)	-1.44	0.150
TG (mmol/L)	1.22 (0.70)	1.20 (0.75)	-0.275	0.783
Glycosylated hemoglobin	5.8 (1.32)	5.6 (0.80)	-1.691	0.091
Random blood glucose (mmol/L)	5.60 (2.11)	5.47 (4.08)	-0.09	0.932
HCY (mmol/L)	19.6 (9.00)	18.4 (8.25)	-0.86	0.388

4.3. Comparison of clinical efficacy before and after treatment between the two groups

The total number of patients in the experimental group who achieved basic recovery, significant improvement, and improvement was 40, with an overall effective rate of 78.43% (40/51). In the control group, the total number of patients who achieved basic recovery, significant improvement, and improvement was 27, with an overall effective rate of 52.94% (27/51). A chi-square test was used to compare the differences between the two groups, and the results were statistically significant (difference in rates: 25.49%, $P < 0.05$). See **Table 5** for details. The proportions of different efficacy levels in the two groups are shown in **Figure 3** and **Figure 4**.

Table 5. Comparison of therapeutic effects before and after treatment between the two groups

Group	Basic cure	Significant progress	Progress	Ineffective	Deterioration	Effective rate	c^2 value	*P* value
Control group	0	6	21	21	3	52.94%	7.35	0.007
Experimental group	0	12	28	9	2	78.43%		

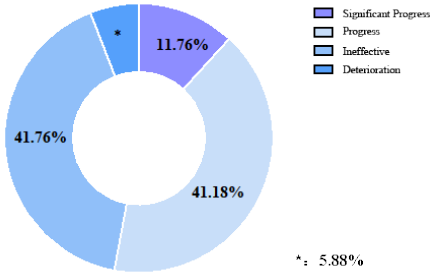

Figure 3. Proportion of different therapeutic effects before and after treatment in the control group.

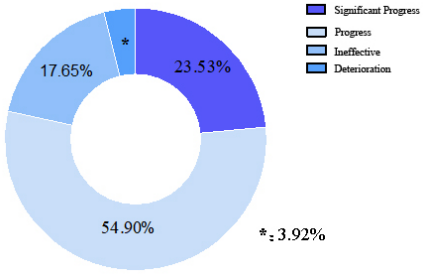

Figure 4. Proportion of different therapeutic effects before and after treatment in the experimental group.

4.4. Comparison of NIHSS score, GCS score, BI score, and mRS score before and after treatment between the two groups

4.4.1. Comparison of NIHSS scores before and after treatment between the two groups

There was no difference in baseline NIHSS levels between the two groups before treatment (t = -0.30, P = 0.766). After 14 days of treatment with edaravone dexborneol in the experimental group, the NIHSS score was lower than that of the control group, and the difference was statistically significant (t = 2.06, P = 0.043). By subtracting the post-treatment NIHSS score from the pre-treatment NIHSS score, the difference in NIHSS was calculated. The difference was greater in the experimental group, and the comparison between the two groups was statistically significant (Z = -2.15, P = 0.032). See **Table 6** for details.

Table 6. Comparison of NIHSS scores before and after treatment between the two groups

Group	Pre-treatment NIHSS	Post-treatment NIHSS	Difference in NIHSS
Control group	12.06 ± 5.22	10.00 ± 5.18*	2.00 (3.75)
Experimental group	12.35 ± 4.72	8.22 ± 3.41#	4.00 (3.50)
t/Z value	-0.30	2.06	-2.15
P value	0.766	0.043	0.032

Note: *P < 0.05 compared to the control group before treatment, #P < 0.05 compared to the experimental group before treatment.

4.4.2. Comparison of GCS scores before and after treatment between the two groups

There was no difference in baseline GCS levels between the two groups before treatment (Z = -0.30, P = 0.766). After 14 days of treatment with edaravone dexborneol in the experimental group, the GCS score was higher than that of the control group, but the difference was not statistically significant (Z = -1.44, P = 0.150). By subtracting the pre-treatment GCS score from the post-treatment GCS score, the difference in GCS was calculated. Although the difference was greater in the experimental group, the comparison between the two groups was not statistically significant (Z = -1.00, P = 0.319). See **Table 7** for details.

Table 7. Comparison of GCS scores before and after treatment between the two groups

Group	Pre-treatment GCS	Post-treatment GCS	Difference in GCS
Control group	15.00 (2.00)	15.00 (1.00)*	0.00 (2.00)
Experimental group	15.00 (3.00)	15.00 (0.00)#	0.00 (2.00)
Z value	-0.30	-1.44	-1.00
P value	0.766	0.150	0.319

Note: *P < 0.05 compared to the control group before treatment, #P < 0.05 compared to the experimental group before treatment.

4.4.3. Comparison of BI scores before and after treatment between the two groups

There was no difference in baseline BI levels between the two groups before treatment (Z = -0.86, P = 0.388). After 14 days of treatment with edaravone dexborneol in the experimental group, the BI score was higher than that of the control group, and the difference was statistically significant (Z = -2.39, P = 0.017). By subtracting the pre-treatment

BI score from the post-treatment BI score, the difference in BI was calculated. The difference was greater in the experimental group, and the comparison between the two groups was statistically significant (Z = -2.48, *P* = 0.013). See **Table 8** for details.

Table 8. Comparison of BI scores before and after treatment between the two groups

Group	Pre-treatment BI	Post-treatment BI	Difference in BI
Control group	20.00 (10.00)	30.00 (15.00)*	10.00 (10.00)
Experimental group	25.00 (20.00)	30.00 (10.00)#	15.00 (15.00)
Z value	-0.86	-2.39	-2.48
P value	0.388	0.017	0.013

Note: **P* < 0.05 compared to the control group before treatment, #*P* < 0.05 compared to the experimental group before treatment.

4.4.4. Comparison of mRS scores before and after treatment between the two groups

There was no difference in baseline mRS levels between the two groups before treatment (Z = -0.60, *P* = 0.550). After 14 days of treatment with edaravone dexborneol in the experimental group, the mRS score was lower than that of the control group, but the difference was not statistically significant (Z = -0.79, *P* = 0.431). By subtracting the post-treatment mRS score from the pre-treatment mRS score, the difference in mRS was calculated. There was no statistically significant difference between the two groups (Z = -0.45, *P* = 0.652). See **Table 9** for details.

Table 9. Comparison of mRS scores before and after treatment between the two groups

Group	Pre-treatment mRS	Post-treatment mRS	Difference in mRS
Control group	4.00 (1.00)	4.00 (0.00)*	0.00 (1.00)
Experimental group	4.00 (0.00)	4.00 (0.00)#	0.00 (1.00)
Z value	-0.60	-0.79	-0.45
P value	0.550	0.431	0.652

4.4.5. Comparison of mRS scores after 90 days of treatment between the two groups

There was no difference in baseline mRS levels between the two groups before treatment (Z = -0.60, *P* = 0.550). After 90 days of treatment, patients' mRS scores were recorded through telephone or outpatient follow-up. The mRS score in the experimental group was lower than that in the control group, and the difference was statistically significant (Z = -2.55, *P* = 0.011). By subtracting the mRS score after 90 days of treatment from the pre-treatment mRS score, the difference in mRS scores was calculated. There was a statistically significant difference between the two groups (Z = -2.08, *P* = 0.038). See **Table 10** for details.

Table 10. Comparison of mRS scores before and after treatment (90 days) between the two **groups**

Group	Pre-treatment mRS	mRS after 90 days	Difference in mRS
Control group	4.00 (1.00)	4.00 (0.00)*	0.00 (1.00)
Experimental group	4.000 (0.00)	4.00 (1.00)#	1.00 (1.00)
Z value	-0.60	-2.55	-2.08
P value	0.550	0.011	0.038

Note: **P* < 0.05 compared to before treatment in the control group, #*P* < 0.05 compared to before treatment in the

experimental group.

4.4.6. Comparison of hs-CRP levels between the two groups of patients

There was no significant difference in the baseline levels of hs-CRP between the two groups before treatment ($t = 1.08$, $P = 0.283$). After treating the experimental group with edaravone dexborneol for 14 days, the level of hs-CRP was lower than that of the control group, and the difference was statistically significant ($t = 3.96$, $P < 0.001$). By subtracting the hs-CRP after treatment from the hs-CRP before treatment, the difference in hs-CRP was obtained, and there was a statistically significant difference between the two groups ($t = -3.65$, $P < 0.001$). See **Table 11** for details.

Table 11. Comparison of hs-CRP scores before and after treatment between the two groups of patients

Group	Pre-treatment hs-CRP	Post-treatment hs-CRP	Difference in hs-CRP
Control group	10.36 ± 1.36	7.26 ± 1.16*	3.09 ± 1.03
Experimental group	10.07 ± 1.25	6.35 ± 1.81#	3.73 ± 0.72
Z value	1.08	3.96	-3.65
P value	0.283	< 0.001	< 0.001

Note: *$P < 0.05$ compared to before treatment in the control group, #$P < 0.05$ compared to before treatment in the experimental group.

4.4.7. Comparison of hospital stay duration and 90-day mortality after treatment between the two groups of patients

The average hospital stay duration for patients in the control group was (17.25 ± 1.59) days, while the average hospital stay duration for patients in the experimental group was (16.90 ± 1.60) days. There was no statistically significant difference between the two groups (difference 0.35, 95% CI -0.27-0.98, $t = 1.12$, $P = 0.266$). The 90-day mortality rate for patients in the control group was 7.84%, while the 90-day mortality rate for the experimental group was 5.88%. There was no statistically significant difference between the two groups ($P = 0.695$). See **Table 12** for details.

Table 12. Comparison of hospital stay duration and 90-day mortality between the two groups of patients

Group	Number of Cases	Length of Hospital Stay	90-Day Mortality Rate
Control group	51	17.25 ± 1.59	4 (7.84%)
Experimental group	51	16.90 ± 1.60	3 (5.88%)
t/c^2 Value		1.12	0.15
P Value		0.266	0.695

4.4.8. Comparison of adverse reactions between the two groups of patients

During the treatment process, indicators such as liver and kidney function, coagulation, and electrolytes were monitored in both groups of patients. In the experimental group, there were 3 cases of hypokalemia (5.88%), which improved after symptomatic treatment with potassium supplementation, and 4 cases of elevated liver transaminases (7.84%), which improved after liver-protecting treatment. There were no adverse events such as rash or dyspnea, and no deaths related to edaravone dexborneol occurred.

5. Discussion

In recent years, stroke has gradually become younger and is a major cause of death and disability. A study in 2016 showed that in China, stroke is the most common disease leading to increased years of life lost for both men and women. A case-control study conducted in 32 countries, including America, Asia, Europe, and Africa, showed that approximately 90% of the population's risk of stroke is associated with factors such as diabetes, physical activity, obesity, and cardiac causes [22]. Large-area cerebral infarction is a severe type of cerebral infarction, with a large range of brain tissue damage that can lead to coma, rapid increase in intracranial pressure, critical illness, high mortality, and most patients will have significant neurological deficits after treatment. Currently, some effective treatment methods can restore blood flow to the brain, such as intravenous thrombolysis, which can dissolve blood clots by activating the fibrinolytic system and exerting anticoagulant effects, thereby improving blood flow to the infarcted area of the brain; endovascular interventional therapy can restore blood flow through mechanical thrombectomy, balloon dilation, and other means, improving prognosis and quality of life. However, due to factors such as insufficient awareness of stroke among the population, treatment time windows, infarcted vessel locations, and thrombolytic contraindications, some patients miss the optimal opportunity for intravenous thrombolysis and endovascular interventional therapy, resulting in a loss of self-care ability and a decline in quality of life. There is an urgent need to explore new treatment methods and approaches based on existing therapies.

5.1. Pathogenesis and characteristics of large-area cerebral infarction

The etiology of large-area cerebral infarction is diverse, primarily including: (1) Atherosclerosis, which is closely related to the occurrence of cerebral infarction. The main cause of large-area cerebral infarction is the formation of in-situ thrombi, and also includes acute complete occlusion of blood vessels due to rupture and bleeding within plaques, although this is relatively rare. (2) Cardiogenic cerebral embolism, which can include air emboli, fat emboli, infectious pus emboli, cancer emboli, etc. The main pathogenic mechanisms include the following: Cardiogenic cerebral embolism caused by atrial fibrillation is the primary cause of cerebral infarction in the elderly. The emboli originate from the left atrial appendage, and atrial fibrillation leads to the formation of red thrombi due to slow blood flow. Patients with rheumatic heart disease develop white thrombi due to irregular and adherent narrow valve surfaces. Patients with acute myocardial infarction develop mural thrombi due to left ventricular myocardial infarction. Cerebral infarction caused by emboli from infective endocarditis is difficult to treat because it is protected by a layer that antibiotics cannot penetrate. Non-bacterial endocarditis can be seen in cancer and autoimmune-related diseases, and the main components of these emboli are platelets and fibrin.

In this study, both the experimental and control groups of patients with large-area cerebral infarction commonly had these two etiologies. Patients with large-area cerebral infarction have severe symptoms and rapid disease progression, often characterized by: (1) The disease course is mostly progressive. Depending on the patient's dominant hemisphere, infarction location, area, collateral circulation, and compensatory status, patients may exhibit different clinical manifestations. Ischemic edema occurs in brain tissue, and midline shift can affect the ascending reticular activating system, leading to consciousness disturbances [23]. (2) Due to the large scope of cerebral infarction and severe ischemia and hypoxia in brain tissue, cytotoxic edema and vasogenic edema can occur in response to harmful stimuli [24]. Additionally, factors such as impeded venous return and acute hydrocephalus can contribute to cerebral edema. Cerebral edema can cause cerebral hernia, leading to worsened consciousness disturbances, pupillary changes, and subsequent decerebrate rigidity and changes in vital signs. If the shifted brain tissue compresses blood vessels, secondary cerebral infarction may occur. During brain tissue shift, sudden pressure changes and the lack of a medial membrane in intracranial large vessels with weak elasticity can potentially tear the vessels, leading to cerebral

hemorrhage [25]. Increased intracranial pressure during cerebral edema can cause projectile vomiting and headache by pulling on the thalamus and pain-sensitive structures in the brain. (3) After a large-area cerebral infarction, patients often become bedridden and unable to care for themselves due to consciousness disturbances, hemiplegia, and other reasons, leading to a series of complications. Some scholars have proposed that the three most common complications are pneumonia (53.5%), electrolyte imbalance (30.9%), and urinary incontinence (18.4%). After multivariate logistic regression analysis, cerebral edema and pneumonia were identified as independent risk factors for poor 3-month prognosis [26]. Patients often die from neurological complications in the early stage of the disease and from medical complications in the later stage.

5.2. The clinical efficacy of edaravone dexborneol in the treatment of large-area cerebral infarction

Edaravone dexborneol injection, approved for marketing in China two years ago, is a Class I innovative drug in our country. Last year, the results of a Phase III clinical trial of edaravone dexborneol in the treatment of acute cerebral infarction were published [27]. The study mainly included patients with onset time within 48 hours, aged 35–80 years old, and NIHSS scores of 4–24. They were randomly divided into an edaravone dexborneol group (n = 585) and an edaravone group (n = 580). The results showed that the edaravone dexborneol group had a greater reduction in mRS scores at 90 days after admission (P = 0.02). When comparing the difference in NIHSS scores before admission and on day 14 of admission, the edaravone dexborneol group had a greater difference (P = 0.01). However, no positive outcomes were obtained in other secondary endpoints (such as the proportion of NIHSS scores ≤ 1 at D14, D30, or D90, and the proportion of BI scores ≥ 95 at D14, D30, D90). Some scholars [17] used alteplase combined with edaravone dexborneol to treat acute cerebral infarction and observed its therapeutic effect. The results showed that the treatment group had a higher effective rate (92.50% vs 72.50%). After treatment, the neurological deficit symptoms and independent living abilities of the study group were better than those of the control group (P<0.05).

Zhang *et al.* [28] conducted a study on the improvement of brain injury by intravenous infusion of edaravone dexborneol in patients with acute anterior circulation cerebral infarction and good endovascular treatment. The results showed that the NIHSS scores of the experimental group were reduced at 2 days, 1 week, and 2 weeks after treatment, and were generally lower than those of the control group (P < 0.05). There was no significant difference in mRS scores between the experimental group and the control group on the 2nd and 7th day of treatment, but the improvement in mRS scores on the 14th day after treatment was significantly better than that of the control group (P < 0.05). However, none of the above studies specifically evaluated the clinical efficacy of edaravone dexborneol in patients with large-area cerebral infarction. In this study, further discussions were conducted on LHI.

In this study, the general information (age, gender, past history, personal history, BMI, infarct side, blood pressure at admission, TOAST classification, intravenous thrombolysis and interventional therapy, mRS score before stroke), laboratory indicators at admission, and NIHSS score, BI score, GCS score, and mRS score before treatment were compared between the two groups of patients. The P-values were all greater than 0.05, indicating no statistically significant difference and suggesting comparability between the two groups. Before treatment, the NIHSS score of the control group was (12.06 ± 5.22), and the NIHSS score of the experimental group was (12.35 ± 4.72). After treatment, the NIHSS score of the control group was (10.00 ± 5.18), and the NIHSS score of the experimental group was (8.22 ± 3.41). Through statistical analysis, it can be concluded that the experimental group can reduce the NIHSS score to a greater extent compared to the control group (P = 0.032). After treatment, patients were compared for clinical efficacy based on NIHSS scores. The effective rate was 52.94% in the control group and 78.43% in the experimental group. Using the chi-square test, P = 0.007 was obtained, indicating that compared with conventional treatment, the addition

of edaravone dexborneol can better improve NIHSS scores in patients with large-area cerebral infarction, resulting in better clinical efficacy.

At the same time, the daily living abilities of the two groups of patients were also evaluated. It was found that after treatment with edaravone dexborneol, the BI score of the experimental group increased more significantly than that of the control group ($P = 0.013$), indicating that edaravone dexborneol can play a positive role in improving patients' daily living abilities. However, when comparing the GCS scores and mRS scores after treatment between the two groups, it was found that although the GCS scores of the experimental group were generally higher than those of the control group, and the mRS scores were generally lower than those of the control group, there was no significant difference between the two groups after statistical testing ($P > 0.05$).

In summary, through comparisons between groups after treatment and differences before and after treatment, it can be concluded that the experimental group has better improvement effects on NIHSS scores and BI scores than the control group, which is consistent with previous research results. However, there was no statistical significance in the comparison of GCS scores and mRS scores between groups and in the comparison of differences, which is inconsistent with the research results of Zhang *et al*. The possible reasons for this may be:

(1) The above researchers included patients with mild acute cerebral infarction who had mild clinical symptoms. However, this study included patients with large-area cerebral infarction who had extensive brain tissue damage and severe neurological deficits. Most patients were bedridden and unable to care for themselves. In the mRS score, level 3 indicates partial assistance and the ability to walk independently, which only a few patients could achieve. Compared with patients with mild acute cerebral infarction, patients with LHI require a longer recovery time. Therefore, the improvement in mRS during hospitalization was not significant.

(2) Consciousness disorders in patients with large-area cerebral infarction may not only be caused by cerebral infarction but also by a combination of multiple factors. The occurrence of cerebral hernia can aggravate or directly cause consciousness disorders. Pulmonary infection can lead to increased consciousness disorders due to inadequate oxygenation. Electrolyte imbalances can also cause consciousness disorders. Therefore, improving oxidative stress and anti-inflammatory responses is only one aspect of improving consciousness disorders in patients with large-area cerebral infarction. More aspects need to be considered, so there was no significant difference in the improvement of consciousness level between the two groups.

(3) This study mainly focused on estimating the sample size for clinical efficacy. To evaluate whether there are statistically significant differences in GCS scores and mRS scores after treatment, a larger sample size may be required. Further evaluation can be conducted with a larger sample size in the future.

5.3. The effect of edaravone dexborneol on hs-CRP

CRP (C-reactive protein, CRP) is a polypeptide molecule primarily synthesized in the human liver. It participates in biological processes such as complement activation, inflammatory responses, and receptor binding. Currently, an immunoassay method can be used to monitor CRP concentrations more sensitively. Through this means, we can measure very low concentrations of CRP, known as hs-CRP. hs-CRP is characterized by structural stability, a long half-life, resistance to hepatic enzyme metabolism, and minimal diurnal variation. As an inflammatory marker, hs-CRP is widely used in various medical research fields. Studies have shown that hs-CRP can directly participate in the formation of atherosclerotic plaques by activating phagocytes and accelerating endothelial cell damage, reducing plaque stability [29]. Zahari et al. found that hs-CRP has a certain predictive effect on cardiovascular events [30] and can guide the prevention of such events. When hs-CRP is at a critical level, even if low-density lipoprotein does not exceed normal levels, oral statin therapy can reduce the risk of myocardial infarction and stroke, with an OR value of 0.53

(95% CI 0.40–0.69, P < 0.00001) [31]. Xiong *et al.* [32] discovered that hs-CRP has diagnostic value for lupus nephritis complicated by urinary tract infection and is also associated with type 2 diabetes mellitus complicated by mild cognitive impairment.

After the occurrence of cerebral infarction, microglia, endothelial cells, and others promote inflammatory responses, and various inflammatory markers in the body increase. Currently, hs-CRP is widely used as an inflammatory marker in studies related to cerebral infarction. hs-CRP can be used to evaluate the severity of acute cerebral infarction and can also affect the occurrence of cerebral infarction. In a follow-up study on the prognosis of stroke, it was found that patients with recurrent cerebral infarction, recurrent heart disease, or death within five years had higher hs-CRP levels than those without recurrence ($P < 0.05$) [33]. Numerous studies have assessed the impact of certain treatments or methods on inflammation levels by comparing hs-CRP levels before and after treatment.

This study found no significant difference in hs-CRP levels between the two groups before treatment ($P > 0.05$). However, after treatment, hs-CRP levels decreased in both groups, and the decrease was greater in the edaravone dexborneol group ($P < 0.05$). This suggests that edaravone dexborneol can better improve inflammation levels in patients with large-area cerebral infarction, consistent with previous research findings. Jiang *et al.* [18] found that edaravone dexborneol had a greater effect on improving oxidative stress levels and inflammatory markers in acute cerebral infarction patients with diabetes ($P < 0.05$). This is one of the reasons why patients in the edaravone dexborneol group had less neurological impairment and better prognosis. Lower hs-CRP levels in patients result in lower levels of various cytokines and adhesion molecules, leading to weaker proinflammatory effects and less damage to vascular endothelium and nerve cells.

5.4. The effect of edaravone dexborneol on the prognosis of large-area cerebral infarction

Currently, there are few studies evaluating the prognosis of cerebral infarction treated with edaravone dexborneol. In the Phase III clinical trial of edaravone dexborneol [27], researchers observed the mRS scores of patients in each group after 90 days of treatment and defined an mRS score of ≤ 1 as functionally independent. Upon comparison, it was found that the proportion of patients with good prognosis was higher in the edaravone dexborneol group ($P = 0.004$). In subgroup evaluations based on gender, NIHSS baseline, etc., female patients achieved better outcomes. Although they were older, their NIHSS scores were lower. There were no significant differences in the results of the other subgroups. In this study, it was found that after 90 days of treatment, the patients' mRS scores were re-evaluated. The overall mRS scores were lower than before treatment, and the reduction was greater in the edaravone dexborneol group ($P < 0.05$). This is consistent with the aforementioned research results, indicating that edaravone dexborneol can improve the short-term prognosis of patients with cerebral infarction. Although the prognosis of patients was generally improved, it did not affect the 90-day mortality rate. There was no significant difference between the two groups. The reason may be that patients with large-area cerebral infarction may have underlying diseases such as hypertension, diabetes, and coronary heart disease. Patients may die from causes such as myocardial infarction or cerebral hemorrhage. If patients are bedridden, they may also die from complications such as pneumonia or venous thrombosis. There are many factors that affect the 90-day mortality rate, and cerebral infarction is just one of them. Therefore, the drug's impact on mortality is not significant.

5.5. The safety of edaravone dexborneol in treating large-area cerebral infarction

In the Phase III clinical trial of edaravone for the treatment of acute cerebral infarction, the most common adverse reactions were found to be elevated liver transaminase levels and skin rashes, but there was no significant difference

between the treatment group and the placebo group [34]. In later clinical trials, it was discovered that edaravone might cause an increase in creatinine levels, but current research results are inconsistent. Currently, dexborneol is rarely used alone to treat diseases, so there are few reports on its adverse reactions. In related studies, the most common adverse reactions of edaravone dexborneol in the treatment of cerebral infarction are elevated liver transaminase levels (5.77%) and hypokalemia (1.66%). Less common adverse reactions include constipation, toothache, headache, chest tightness, dizziness, and difficulty falling asleep [27]. In this study, there were 3 cases of hypokalemia and 4 cases of elevated liver transaminase levels in the edaravone dexborneol group, but they improved after treatment. There were no adverse reactions such as elevated creatinine levels or skin rashes, and no drug-related deaths occurred. Therefore, it can be proven that edaravone dexborneol is safe and effective in the treatment of large-area cerebral infarction.

Disclosure statement

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