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Original Article

The effect of edaravone on subcortical cerebral infarction patients and the risk of neurological deterioration

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Abstract: Objective: To explore the effect of edaravone in subcortical cerebral infarction patients and to analyze the risk factors for neurological function deterioration. Methods: A total of 108 subcortical cerebral infarction patients were recruited for this prospective study and divided into two groups, with 54 cases in each group. The control group received the conventional treatment, and the observation group received the conventional treatment and edaravone, 30 mg via an intravenous drip, twice a day for 14 days. The effects of the two treatments on the two groups were observed. The endothelial function (endothelin-1, intercellular adhesion molecule-1, and nitric oxide), the inflammatory factors (C-reactive protein, tumor necrosis factor α, and interleukin-6), the oxidative stress (advanced oxidation protein products, malonaldehyde, and superoxide dismutase) levels, and the cognitive function indicators were measured. The risk of neurological function deterioration was analyzed. Results: The total effective rate in the observation group was higher than it was in the control group (P=0.026). The improvement in the endothelial function, inflammatory factors, oxidative stress levels, and cognitive function in the observation group was better than it was in the control group (all P<0.05). Hypertension, abdominal obesity, and low education level are independent risk factors for subcortical infarction vascular cognitive impairment (all P<0.05). Conclusion: Edaravone is effective in the treatment of subcortical cerebral infarction and may work by improving oxidative stress levels, reducing the inflammatory factors, and improving endothelial function. Hypertension, abdominal obesity and low education level are independent risk factors for subcortical infarction vascular cognitive impairment in patients with subcortical cerebral infarction.

Keywords: Edaravone, subcortical cerebral infarction, clinical efficacy, risk factors

Introduction

Cerebral infarction is a type of cerebral ischemic stroke (CIS) and is caused by insufficient blood supply to the brain and ischemia and hypoxia in brain tissue with a varied etiology that results in damage to the brain's nerve function [1, 2]. The annual incidence of cerebral infarction is on the rise, 30% of the patients who suffer from the condition are elderly, and it has high mortality and disability rates [3-6]. About 11.4%-14.5% of patients with acute cerebral infarction (ACI) die within one year, and ACI has become the leading cause of death in China [7]. Subcortical cerebral infarction is a kind of cerebral microvascular disease and a common clinical type of cerebral infarction, and it accounts for about 25% of CIS cases. Early asymptomatic cerebral infarction is difficult to find and diagnose. Studies have shown that subcortical cerebral infarction can easily lead to cognitive impairment, which is clinically referred to as subcortical ischemic vascular cognitive impairment (SIVCI) [8, 9]. Patients with SIVCI have abnormal cognition, behavior, and movement caused by the interruption of the cortex and subcortical connection induced by the subcortical infarction focus. Some studies have found that the frontal cortex in SIVCI is significantly thinned, leading to damage to the frontal executive function [10, 11].

Edaravone is a common auxiliary drug for the clinical treatment of cerebral infarction. Clinical studies have found that Edaravone can

scavenge oxygen free radicals, enter the blood-brain barrier, reduce nerve cell damage, and reduce the infarction area [12]. A study used edaravone to treat rats with vascular dementia induced using chronic cerebral hypoperfusion and the authors found that the morphology of the neurons in the rats' cerebral ischemia areas was significantly improved compared with the control group, and the number of nuclear factor E2 related to stress and cognition was increased, suggesting that edaravone can effectively improve the oxidative stress levels and the cognitive function of vascular dementia rats [13]. At present, there is no published clinical study on the use of edaravone in subcortical cerebral infarction patients. To fill this gap, this study examines the clinical efficacy and related mechanism of edaravone in patients with subcortical cerebral infarction and studies the causes of neurological function deterioration.

Materials and methods

Clinical materials

With the approval of our hospital's ethics committee, a total of 108 patients in the Department of Neurology of Shidong Hospital of Yangpu District were recruited for this study from January 2017 to June 2019 and randomly divided into two groups. 54 patients were placed in the control group and received the conventional treatment, and 54 patients were placed in the observation group and received the conventional treatment combined with edaravone injections. All the patients or their families included in this study signed a written consent form.

Inclusion criteria

(1) Patients who met the diagnostic criteria for subcortical cerebral infarction in acute cerebral infarction [14], (2) patients with an onset time within 24 hours, (3) patients ranging in age from 18-76 years old, (4) patients diagnosed with single subcortical cerebral infarction for the first time, (5) patients who were awake at the time of admission, (6) and patients with a cerebral infarction scale (NIHSS) score ranging from 5-15 points [15].

Exclusion criteria

(1) Patients allergic to edaravone, (2) patients with a history of craniocerebral injury or cerebrovascular disease, (3) patients unable to cooperate with the cognitive function evaluation, (4) patients with dementia or cognitive impairment before the treatment, (5) patients with a malignant tumor, (6) patients with a mental illness that affects their cognition.

Methods

Control group: The patients in the control group received the conventional treatment, which included monitoring their vital signs, routine oxygen inhalation, thrombolysis, anticoagulation, lipid regulation, and plaque stabilization [14].

Observation group: The patients in the observation group received the conventional treatment plus edaravone (Nanjing Xiansheng Donglin Pharmaceutical Co., Ltd., China), through a 30 mg intravenous drip, twice a day for 14 days.

Outcome measures

Primary outcomes: One month after the treatment, the clinical efficacy was evaluated according to the NIHSS criteria: cured, effective, progress, or invalid [15]. The total effective rate (%) = (the case number of cure + effective + progress)/total number of cases * 100.

Two tubes of 5 mL venous blood were collected once before the treatment and at 14 days after the treatment. The serum endothelin-1 (ET-1), intercellular adhesion molecule-1 (ICAM-1), serum C-reactive protein (CRP), serum tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), advanced oxidation protein products (AOPP), malonaldehyde (MDA), and superoxide dismutase (SOD) levels were determined using a serum enzyme-linked immunosorbent assay. The nitric oxide (NO) level was determined using micro colorimetry. The assay kits were all from the Shanghai Enzyme-Linked Biology Co., Ltd.

Secondary outcomes: The Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) were used to evaluate the cognition before and after the treatment, and the total possible MMSE and MoCA scores

Table 1. Comparison of the general patient data

Item	Observation group (n=53)	Control group (n=52)	χ^2/t	P
Gender			0.229	0.632
Male	32	29		
Female	21	23		
Age (years)	67.1±7.5	67.9±7.1	0.561	0.576
Education level (years)	11.2±4.4	11.4±4.3	0.236	0.814
Stroke site			0.605	0.895
Thalamus	13	11		
Frontal lobe	6	8		
Internal capsule	5	6		
Basal ganglia region	29	27		
Complication				
Hyperlipidemia (yes/no)	33/20	31/21	0.077	0.781
Hypertension (yes/no)	38/15	34/18	0.485	0.486
Coronary artery disease (yes/no)	16/37	19/33	0.476	0.490
Abdominal obesity (yes/no)	20/33	22/30	0.229	0.633
Hyperhomocysteinemia (yes/no)	41/12	42/10	0.184	0.668
Hyperuricemia (yes/no)	29/24	27/25	0.082	0.774

were 30. Lower scores indicated poor cognitive function in a patient [16].

The patients were followed up at their visits to the clinic or by telephone for one year, and they were divided into SIVCI and non-SIVCI groups according to whether they met the diagnosis of SIVCI issued by the Chinese Guidelines for Diagnosis and Treatment of Vascular Cognitive Impairment (2016) [17]. Deterioration of neurological function means that the National Institutes of Health Stroke Scale (NIHSS) score increased by 4 or more points or the patient died, and the risk of neurological function deterioration were studied.

Statistical methods

SPSS 17.0 was used to analyze the data. The measurement data were expressed as the means ± standard deviation ($\bar{x}$ ± sd); the data conforming to a normal distribution and homogeneity of variance were analyzed using independent sample t tests, which were expressed as t; and the data not conforming to a normal distribution or homogeneity of variance were analyzed using rank sum tests, which were expressed as M (P25, P75). The count data was expressed as the number of cases and percentage (n/%) and were tested using the Pearson's chi-square tests, and were expressed as χ^2. The factors influencing vascular cognitive impairment were analyzed. The dependent variable was the occurrence of vascular cognitive impairment, and the factors with significant differences between the two groups were included in the variable, and the step-by-step method was used to construct a multifactor logistic regression model. P<0.05 was considered statistically significant.

Results

Comparison of the general data

There was 1 patient in the observation group and 2 in the control group who withdrew because of they were lost to follow-up. There were no significant differences in terms of the general clinical data between the two groups (P>0.05). See **Table 1**.

Comparison of the curative effects

The total effective rate of the observation group was higher than it was in the control group (P<0.05), as shown in **Table 2** and **Figure 1**.

Comparison of the related indexes before and after the treatment

After the treatment, the ET-1, ICAM-1, CRP, TNF-α, IL-6, MDA, SOD, and AOPP levels in the two

Table 2. Comparison of the curative effects (n/%)

Item	Observation group (n=53)	Control group (n=52)	χ^2	P
Cure	5 (9.43)	3 (5.77)	8.729	0.033
Effective	26 (49.06)	13 (25.00)		
Progress	12 (22.64)	16 (30.77)		
Invalid	10 (18.87)	20 (38.46)		
Total efficiency (%)	43 (81.13)	32 (61.54)	4.938	0.026

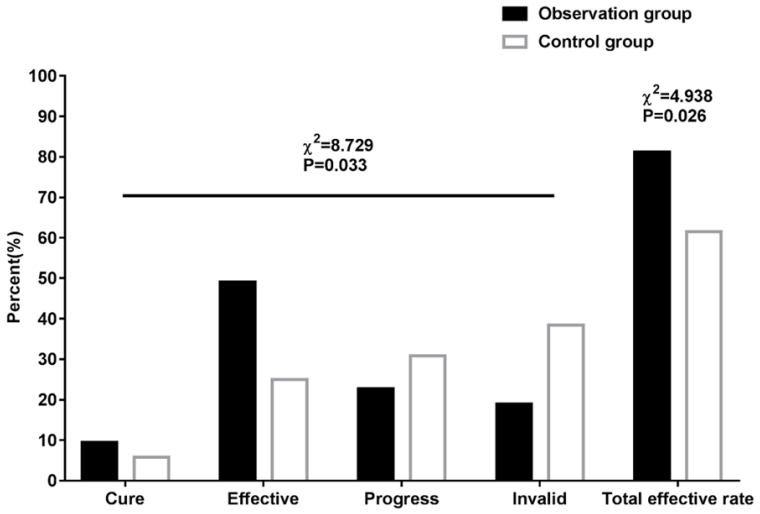

Figure 1. Comparison of the curative effects.

groups decreased, but the NO level increased (P<0.05). After the treatment the above indexes in the observation group were at better levels than the corresponding indexes in the control group (all P<0.05), as shown in **Table 3**.

Comparison of the cognitive function before and after the treatment

After the treatment, the MMSE and MoCA scores in both groups were significantly improved compared with the scores before the treatment, and the MMSE and MoCA scores in the observation group were higher than the scores in the control group (P<0.05), as shown in **Table 4**.

The risk factors for vascular cognitive impairment

Among the 105 patients with subcortical cerebral infarction, 35 developed SIVCI and were enrolled in the SIVCI group, and the other 70 patients were enrolled in the non-SIVCI group. In the SIVCI group, the patients had lower education levels and higher incidences of hyperlipidemia, hypertension, abdominal obesity, and hyperhomocysteinemia (all P<0.05), as shown in **Table 5**.

Multivariate logistic regression analysis of SIVCI in patients with subcortical cerebral infarction

A multivariate regression analysis showed that hypertension, abdominal obesity, and education levels were independent risk factors for SIVCI in patients with subcortical cerebral infarction (all P<0.05), as shown in **Tables 6** and **7**.

Discussion

Clinically, SIVCI is the major type of vascular dementia. Patients suffering from subcortical cerebral infarction should pay close attention to any changes in their cognitive function. If they can't receive effective intervention and eliminate the related risk factors, their cognitive function may decline [8, 9]. Studies have shown that the brain promotes the oxidative stress under ischemia and hypoxia. Under the stimulation of oxidative stress, the hippocampal blood vessels are reshaped, leading to vascular lumen stenosis and microvascular smooth muscle thickening, so as to impact the spatial memory function [18]. Edaravone, a brain protective agent, can inhibit oxidative stress. Animal experiments have found that the learning and memory abilities of rats with cognitive decline caused by cerebral ischemic diseases were improved to varying degrees after treatment with edaravone [19]. Another study showed that edaravone treatment in rats with chronic cerebral ischemia can reduce the oxidative stress levels in the brain, repair damaged neurons, and improve the rats' spatial and fear memories [20]. Our study also found that edaravone can improve the patients' nerve injuries and cognition, which may be related to edaravone's ability to repair damaged neurons.

Table 3. Comparison of the related indexes before and after the treatment ($\bar{x}$ ± sd)

Item	Before treatment		After treatment	
	Observation group (n=53)	Control group (n=52)	Observation group (n=53)	Control group (n=52)
ET-1 (pg/L)	9.72±3.44	9.64±3.68	3.69±1.34$^{**,\#\#\#}$	5.58±1.39*
NO (mmol/L)	1.76±0.82	1.74±0.87	3.95±1.62$^{***,\#\#\#}$	2.63±1.27***
ICAM-1 (mg/L)	387.52±53.23	382.89±57.81	275.39±26.89$^{***,\#\#\#}$	318.92±31.45***
CRP (mg/L)	6.63±1.95	6.81±1.72	4.76±1.53$^{**,\#\#\#}$	5.63±1.52*
TNF-α (μg/mL)	123.87±18.62	123.98±18.19	86.88±14.91$^{***,\#\#\#}$	104.18±16.54***
IL-6 (μg/mL)	387.52±37.21	382.76±37.81	269.39±37.89$^{***,\#\#\#}$	318.92±52.45***
MDA (mg/L)	23.68±2.82	23.89±3.46	7.76±2.26$^{***,\#\#\#}$	13.67±2.32***
SOD (ng/L)	188.08±1.27	188.32±1.35	121.15±5.16$^{***,\#\#\#}$	154.76±5.48***
AOPP (ng/L)	55.31±7.35	56.53±6.31	22.45±1.92$^{***,\#\#\#}$	33.65±2.23***

Note: Compared with the same group before the treatment, *P<0.05, **P<0.01 and ***P<0.001; Compared with the control group after the treatment, $^{\#\#\#}$P<0.001. ET-1: endothelin-1; NO: nitric oxide; ICAM-1: intercellular adhesion molecule-1; CRP: C-reactive protein; TNF-α: tumor necrosis factor α; IL-6: interleukin-6; AOPP: advanced oxidation protein products; MDA: malonaldehyde; SOD: superoxide dismutase.

Table 4. Comparison of the cognitive scores before and after the treatment ($\bar{x}$ ± sd)

Item	Observation group (n=53)	Control group (n=52)	t	P
MMSE (grade)				
Before treatment	25.56±1.24	25.41±1.18	0.670	0.504
After treatment	27.87±0.93*	25.74±1.82	7.991	<0.001
MoCA (min)				
Before treatment	22.52±1.99	22.25±2.38	0.666	0.507
After treatment	23.76±2.06*	22.25±2.17	3.681	<0.001

Note: Compared with the same group before the treatment, *P<0.05. MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination.

The state of oxidative stress, the release of the inflammatory factors in the brain, and the endothelial dysfunction caused by cerebral vascular endothelial injuries are all related to the occurrence and development of cerebral infarction [21-24]. Previous studies have shown that edaravone may improve cognitive function and the level of oxidative stress during cerebral ischemia and hypoxia through the activation of the Nrf2 signal pathway to increase the levels of SOD and heme oxygenase-1 in the brain. Then the level of MDA is decreased and the level of defense against oxidative stress in the brain is increased. Meanwhile, oxidative stress and the release of the inflammatory factors are inhibited [19, 25]. In addition, edaravone can inhibit the apoptosis of oligodendrocytes under cerebral ischemia and hypoxia, reduce injury to the white matter and the vascular endothelium to protect nerve cells and improve cognitive function [26, 27]. In our study, patients treated with Edaravone had an improved state of oxidative stress, decreased the release of inflammatory factor, and their endothelial function recovered to normal level to reduce nerve injury and improve cognition.

Our follow-up work found that some patients gradually developed a vascular cognitive impairment over time, which can progress to dementia and affect patients' quality of life. We also found that hypertension, abdominal obesity, and education level were independent risk factors for the occurrence of SIVCI in patients with subcortical cerebral infarction. Some studies have found that hypertension is a risk factor for vascular dementia. Patients with a systolic blood pressure 120 mmHg are less likely to develop dementia and microvascular diseases than those with 140 mmHg [28]. Previous studies also reported there is a significant increase in the incidence of brain atrophy and the risk of dementia in middle-aged people with abdominal obesity [29, 30]. There is a negative relationship between years of education and cognitive impairment [31]. In our study, the results showed that edaravone can improve patients' cognition in the short term, but it was not determined in the long term whether edaravone is a risk factor for cognitive

Table 5. Comparison of the related data (n, $\bar{x} \pm sd$)

Item	SIVCI group (n=35)	Non-SIVCI group (n=70)	χ^2/t	P
Gender			0.489	0.484
Male	22	39		
Female	13	31		
Age (years)	67.8±7.7	67.3±7.2	0.328	0.744
Education level (years)	10.2±4.3	12.1±4.5	2.069	0.041
Stroke site			6.334	0.069
Thalamus	13	11		
Frontal lobe	3	11		
Internal capsule	3	8		
Basal ganglia region	16	40		
Combined disease				
Hyperlipidemia (yes/no)	29/6	34/36	11.429	0.001
Hypertension (yes/no)	30/5	42/28	7.159	0.007
Coronary artery disease (yes/no)	12/23	23/47	0.021	0.884
Abdominal obesity (yes/no)	29/6	13/57	40.179	<0.001
Hyperhomocysteinemia (yes/no)	32/3	51/19	2.986	0.042
Hyperuricemia (yes/no)	19/16	37/33	0.019	0.890
Thrombolysis (yes/no)	20/15	42/28	0.079	0.779
Treatment with Edaravone (yes/no)	15/20	38/32	1.219	0.270

Note: SIVCI: subcortical infarction vascular cognitive impairment.

Table 6. Independent variable assignment table of the risk factors for SIVCI in patients with subcortical cerebral infarction

Factor	Independent variable	Assignment
Hyperlipidemia	X1	Yes =1, no =0
Hypertension	X2	Yes =1, no =0
Abdominal obesity	X3	Yes =1, no =0
Hyperhomocysteinemia	X4	Yes =1, no =0
Education level	X5	

Note: SIVCI: subcortical infarction vascular cognitive impairment.

impairment, which may be due to the small sample size of this study. As time progresses, the proactive effect of edaravone may be weakened, and the risk factors can still have negative impacts, hence cognitive impairment may still occur in patients with subcortical cerebral infarction.

However, there are some limitations to our study. For example, this study is a single-center study, and it did not focus on the efficacy of different doses of Edaravone in patients with subcortical cerebral infarction. Patients with subcortical cerebral infarction have different clinical symptoms at different infarct sites, but this study does not focus on the therapeutic effect of edaravone on patients with different infarction sites. Therefore, a multi-center study with a large cohort is needed to validate our findings.

In conclusion, edaravone is effective in the treatment of subcortical cerebral infarction and may work by improving the state of oxidative stress, reducing the inflammatory factor levels, and improving endothelial function. Hypertension, abdominal obesity, and education level are independent risk factors for SIVCI in patients with subcortical cerebral infarction.

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Table 7. Multivariate logistic regression analysis of SIVCI in patients with subcortical cerebral infarction

Factor	β	SE	Wald value	Adjusted OR value (95% CI)	P
Hyperlipidemia	0.098	0.034	0.821	1.132 (0.957-1.432)	0.687
Hypertension	1.421	0.571	12.439	3.123 (2.931-7.565)	<0.001
Abdominal obesity	0.867	0.262	4.172	2.164 (1.278-3.732)	0.038
Hyperhomocysteinemia	0.069	0.029	0.712	1.019 (0.978-1.081)	0.715
Education level	0.906	0.269	4.165	2.164 (1.315-3.743)	0.022

Note: OR: odds ratio; CI: confidence interval; SIVCI: subcortical infarction vascular cognitive impairment.

Disclosure of conflict of interest

None.

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