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Original Article

The clinical efficacy and safety of edaravone combined with GM1 in the treatment of the elderly patients with cerebral infarction

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Abstract: Objective: To evaluate the clinical efficacy and safety of edaravone combined with GM1 in the treatment of the elderly patients with cerebral infarction. Methods: The data is collected from patients treated in our hospital from June 2012 to June 2015. They were randomly divided into treatment group of edaravone combined with GM1 (group A, 50 cases) and treatment group of GM1 (group B, 50 cases). After four-week treatment, the changes of NHISS scores were evaluated before and after treatment, and adverse reactions of patients were observed and recorded. Result: Before treatment, NHISS scores of the two groups were similar. After treatment, compared with those of before-treatment, NHISS scores of the two groups both decreased sharply. The discrepancy provedto have statistical significance ($P<0.05$). Moreover, NHISS scores of group A, at 9.01±2.16, were obviously lower than those of group B, at 13.61±3.06, which also had the statistical significance ($P<0.05$). The overall efficiency of group A (84%), was sharply higher than that of group B (60%), which was of the statistical significance ($P<0.05$). During the course of treatment, two patients had adverse reactions, one in group A and the other in group B. Conclusion: The treatment of edaravone combined with GM1 could significantly alleviate the clinical symptoms of patients with cerebral infarction, especially having a significant effect for the recovery of neurological function, and it also held high safety with low side effects. Therefore, this method could be used into more applications extensively in clinical treatment.

Keywords: Edaravone, GM1, cerebral infarction, clinical efficacy

Introduction

With the problem of aging population, the incidence rate of senile diseases is getting much higher than ever before, which has exerted a severe impact on health of the whole population in China, especially on the physical and mental health of the aged. Cerebral ischemia is one of the most common senile diseases characterized by high incidence, and high rates of disability and death [1]. In 2013, the World Health Organization announced that cerebral ischemia had been one of the ten top diseases which could cause death. There are more than 6 million people dying from cerebral ischemia all over the world per year, accounting for about 10.6% of the total morality [2]. The investigation of Chinese epidemiology showed the incidence of cerebral ischemia was around 12% among the aged over 60 years old at WanShou Road District of Beijing in China [3]. Thus, cerebral infarction is severely damaging the patients' living quality. Ischemic cerebral infarction is a common type of brain infarction disease. At present, thrombolysis is the clinically the main first-line treatment, but there are time limitations on its medication. Generally speaking, thrombolysis therapy needs to be performed within six hours since the onset. However, clinically, many patients have missed the best treatment time when they arrived at the hospital.

Neuroprotective agents can overcome the time restriction so that doctors can provide better treatment protocols for patients. In recent years, studies have shown that the neural protectants, such as [4, 5]. Edaravone and GM1,

had certain therapeutic efficacy on nerve injury caused by ischemic cerebral infarction. Edaravone has been able to inhibit the oxidation of low density lipoprotein and prevent the cells from releasing excessive high mobility group protein. As a result, the nerve cells would be improved, and the damages in the nerve cells and blood vessel would be alleviated. GM1 can not only effectively block the ischemic cascade reaction but also improve the recovery of the injured nerves. However, trials have shown that [6, 7], GM1 alone could not effectively treat ischemic cerebral infarction. In addition, trials on animals suggested [8] that GM1 used in combination with other neuro -protective agents could be better neural protection

At present, clinical reports on GM1 combined by other neuroprotective agents in the treatment of ischemic cerebral infarction are rare. And its clinical efficacy and safety are still uncertain. In this study, we attempted to combine GM1 with edaravone in the treatment of ischemic cerebral infarction in elderly patients, and evaluated its clinical efficacy and safety to bring some insight into optimizing clinical protocols of ischemic cerebral infarction in the future.

Materials and methods

General information

Inclusion criteria: Patients (over the age of 60 years) with ischemic cerebral infarction, within 12h from the onset. Exclusion criteria: Patients with severe liver and renal failure or heart failure and other serious diseases; patients who took medicine irregularly or stopped taking halfway and those who could not complete the treatment with full cooperation or could not provide complete information.

This study included 100 cases of elderly patients with ischemic cerebral infarction being hospitalized in our hospital from June 2012 to June 2015 as the subjects in the study. Among them, 65 cases were male and 35 were female, ranging in age from 61 to 88 years old with an average of (71.09±10.39) years. The patients were randomized into 2 groups: Group A (n=50) and group B (n=50). Patients in Group A were treated with edaravone combined with GM1, while those in Group B were treated with GM1 only. This study was approved by the Ethics Committee of our hospital, all the subjects or their families signed informed consent before treatment.

Treatment methods

Treatment methods were as follows: Firstly, the patients in the two groups were provided with symptomatic therapy, including the control of blood glucose level and blood pressure level. They were also given with dehydration and lipid-lowering therapy, using conventional Aspirin Enteric-coated Tablets and Rosuvastatin Calcium Tablets in anti-platelet aggregation and anti-atherosclerosis therapy. On that basis, Group B was provided with GM1 (100 mg)+0.9% Sodium Chloride Injection (250 ml) once a day; Group A received, in addition to the same treatment as that of Group B, intravenous drip of edaravone at 60 mg per day. All the subjects in the two groups were treated with Neuro protectants within 12 hours after the onset, and the medication duration was 4 weeks.

Curative properties observation

The changes of neurological functions before and after the treatment were evaluated in accordance with NIHSS Scoring criteria [9].

According to the NIHSS scores, the clinical efficacy was divided into 6 grades. 90%-100% reduction in the score was regarded as basic healing; 18%-45% reduction in the score as progress; 46%-89% as significant progress; reduction or less than 18% increase in the score as no change and more than 18% increase in the score or death as getting worse. The efficiency of treatment was the sum of basic healing, significant progress and progress. In order to evaluate the overall efficiency, the calculation formula was as follows: (NIHSS scores before treatment-NIHSS scores after treatment)/NIHSS scores before treatment * 100%.

The observation of adverse reaction, including death, severe disability or severe impairment of the functions of liver and kidney occurring during the medication treatment should be recorded in time, no matter whether they were related to the drug treatment or not.

Statistical principle

Statistical analysis was performed by SPSS 19.0. $\bar{x}\pm S$ was used to express normal distribution measurement data; the independent sam-

Table 1. The contrast of general information, diseased region and elements of risk of the patients in two groups

		Group A (n=50)	Group B (n=50)	*P*
General information	Age (annum)	73.01±9.81	70.12±10.31	0.281
	Gender (man/women)	31/17	34/18	0.366
	NIHSS score before treatment	17.39±2.06	18.61±1.88	0.471
Elements of risk	Hypertension (example)	31	29	0.339
	Hyperlipoidemia (example)	41	38	0.461
	Smoking (example)	26	21	0.566
	Drinking (example)	31	33	0.219
Diseased region	Cerebral lobes (example)	21	19	0.226
	Basal ganglia (example)	11	12	0.433
	Brainstem (example)	12	12	0.371
	Cerebellum (xample)	6	7	0.269

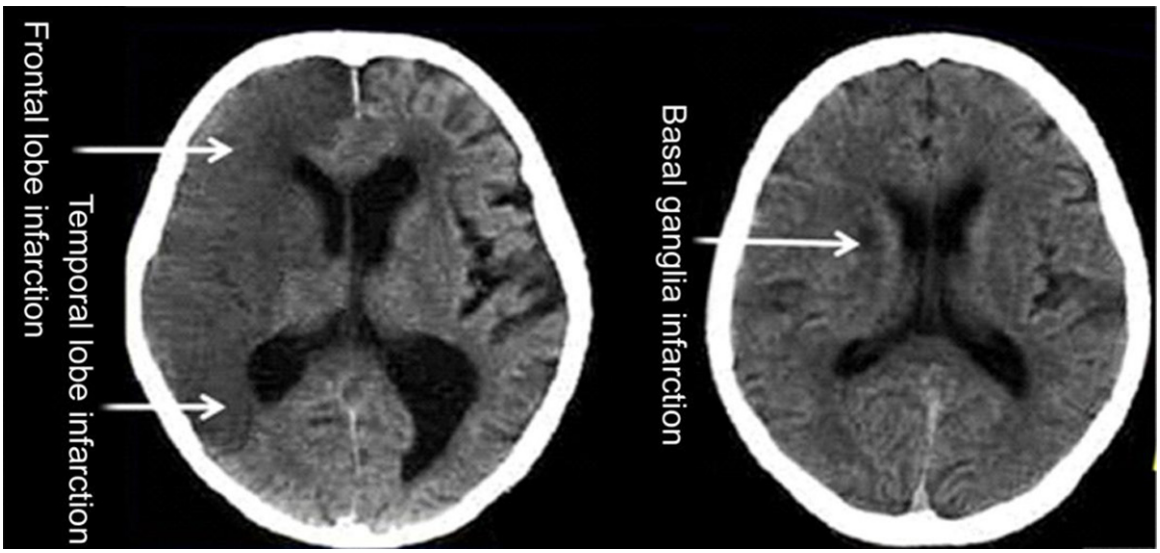

Figure 1. The blocked parts of cerebral lobes and basal ganglia.

Table 2. The comparison of the NHISS score of the patients in two groups after treatment

Group	Number	Prior treatment score	Post-treatment score
A	50	17.39±2.06	9.01±2.16*/**
B	50	18.61±1.88	13.61±3.06*

Note: *P<0.05, compared with prior treatment; **P<0.05 compared with Group B.

ples test was performed for the comparison between the two groups, and the example number or percentage was adopted to present the count data. The comparison of the two groups was tested by χ^2 test or Fisher exact probability method, P<0.05 indicated that the difference was of statistically significance.

Results

The contrast of general information, diseased region and elements of risk of the patients in the two groups

As shown in **Table 1**, the general information of the patients being compared between the two groups include gender, age and NIHSS scores before treatment, and the difference was not statistically significant (P>0.05). As for the elements of risk, there was no statistically significant difference (P>0.05) in hypertension, hyperlipoidemia, smoking and drinking. In addition, there was also no statistically significant difference in the diseased regions between the two groups. The blocked parts of the patients in

Table 3. The comparison of clinical efficacy of patients in two groups after treatment

Group	Basic recovery	Significant progress	Progress	NC	Deterioration	Total effective rate
Group A (n=50)	20	12	10	7	1	84%
Group B (n=50)	12	10	8	18	2	60%

both groups mainly appeared in the cerebral lobes (as shown in **Figure 1**), basal ganglia (as shown in **Figure 1**), brainstem and cerebellum, and the difference was also not statistically significant (P>0.05).

The comparison of the NHISS scoresbetween the two groups before and after treatment

The NHISS scoresafter treatment, compared with those before treatment, decreased significantly in both groups, and there was statistically significant difference (P<0.05). Further analysis showed that the NHISS scores of treatment by edaravone combined with GM1 was significantly lower than that byonly GM1, and there was statistically significant difference (P<0.05), as shown in **Table 2**.

The comparison of clinical efficacy of the patients betweenthe two groups after treatment

The comparison of clinical efficacy of the patients between the two groups after treatment showed that the efficiency of treatment by edaravone combined with ganglioside GM1 was obviously higher than that by ganglioside GM1 alone, and there was statistically significant difference (P < 0.05), as seen in **Table 3**.

Adverse reactions

In the course of the treatment, two patients had adverse reactions of liver injury. One was in the treatment group of edaravone combined with GM1 and the other was in the GM1 treatment group. And they both returned to normal after treatment.

Discussion

With the rapid development of China's economy and the improvement of people's living standard, the incidence of cerebral infarction, which is one of the most common causes of death inelderly patients, has greatly increased. Clinically, ischemic stroke is the most frequent condition in cerebral infarction. The study showed that [10, 11] the causes for cerebral infarction were very complex, including hypertension, high cholesterol and coronary heart disease. The thrombolytic therapy frequently used in clinical practiceis too restrictive intime. At the same time, it does not have a great efficacy on patients. Although some neuroprotective agents such as edaravone or GM1 has some therapeutic effects on the nerve disorders caused by the ischemic infarction, the efficacy by a single drug is limited. Therefore, we tried to treat ischemic infarction by combined therapy, hoping to alleviate the clinical symptoms of the patients and improve their health.

The results showed that both the GM1 protocol and the one combined edaravone with GM1 significantly reduced the NIHSS scores of the ischemic stroke patients. But after treatment, the NHISS scores bythe edaravone combined with GM1 treatment were obviously lower than thoseof the GM1 group, indicating that edaravone combined with GM1 hadthe synergistic effects and could effectively alleviate the ischemic neurological symptoms of patients with cerebral infarction, accelerating the course of recovery. The combined medication of edaravone and GMI is advantageous in the treatment of ischemic stroke [12-17] that it can block brain tissues being destructed by ischemia and decrease apoptosis of brain cells, so that it can promote the recovery of the nerve functions. What's more, it can suppress the expression of vascular endothelial cells, reducethe oxidation of LDL and regulatethe apoptosis-related genes to reduce the damage and apoptosis of nerve cells. GM1 is capable of antagonizing neurotoxicity, correcting ion imbalances, inhibiting apoptosisand promoting the nerve repair. Previous studies have shown that [18] edaravone combined with GM1 treatment had good effect on improving the patient's neurological dysfunction and neurological repair, which is consistent with our results.

In addition, we've found that the group byedaravone combined with GM1 has a much higher total efficiency than the treatment group by only GM1, indicating that using edaravone com-

bined with GM1 medication to treat Ischemic Cerebral Infarction clinically has better effects on improving the patient's neurological dysfunction and neurological repair and improving patients' living quality. Further illustration from this study is that the synergistic effects of the combination of edaravone with GM1 can stop a series of cascade reactions, reduce the damages of cerebral neurons and brain tissue to alleviate patients' symptoms and promote the recovery of neurological functions [19-23]. However, its underlying mechanisms need to be further proved. As for safety, two patients in our study had adverse reaction of the liver dysfunction, each from the two groups. And both of the patients were cured after treatment. Therefore, the edaravone combined with GM1 medication was proved to have acceptable safety and little severe side effects.

There are deficiencies in this study, including (1) the insufficiency in the number of cases collected, (2) the limited age groups (only elderly patients), (3) the lack of optimization in therapeutic dosage and therapeutic time in edaravone combined with GM1 medication. In the future, we'll enlarge the sample size and the range of subjects, optimizing therapeutic dosage and therapeutic time in combined use of neuroprotective agents to improve the clinical efficacy on Ischemic Cerebral Infarction and its long-term prognosis.

In summary, the treatment using edaravone combined with GM1 can function well in improving the neurological dysfunction and Ischemic Cerebral Infarction of patients. This treatment can improve the patient's living quality and reduce the burden of families and society. Meanwhile, it was proved to be in safety and had good clinical efficacy; therefore, it is worthy of being extensively used in clinical practice and can bring some insight on the optimization of protocols for Ischemic Cerebral Infarction.

Disclosure of conflict of interest

None.

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