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Effectiveness of alteplase intravenous thrombolysis combined with butylphthalide in patients with acute severe cerebral infarction

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Abstract

Introduction: *The aim of the study was to investigate the effectiveness of alteplase intravenous thrombolysis combined with butylphthalide in patients with severe cerebral infarction.*

Material and methods: *From February 2018 to March 2019, 100 patients with severe cerebral infarction in Rongcheng People's Hospital were recruited and randomly divided into two groups, i.e., alteplase intravenous thrombolysis treatment group and alteplase intravenous thrombolysis combined with butylphthalide treatment group. The efficacy of treatment methods was compared between the two groups by analyzing National Institutes of Health Stroke Scale (NIHSS) scores of patients on the first, seventh, and fourteenth days after treatment. Quality of life of patients was evaluated using Barthel scale before and after treatment, and also, the incidence of adverse reactions was compared between the two groups.*

Results: *The therapeutic effect and quality of life in the alteplase intravenous thrombolysis combined with the butylphthalide group were better compared with patients in the alteplase intravenous thrombolysis group. The total effective rate of the alteplase intravenous thrombosis group was 80%, and that of the alteplase intravenous thrombosis combined with butylphthalide group was 100%; the latter treatment was more effective ($p < 0.05$). NIHSS scores of the patients at 1, 7, and 14 days after treatment were better in the former group than in the latter ($p < 0.05$). Moreover, the probability of adverse reactions in the alteplase intravenous thrombosis group was 6%, and the probability of adverse reactions in the alteplase intravenous thrombosis combined with butylphthalide group was 4%. The incidence of adverse reactions in the former group was similar to that in the latter ($p > 0.05$). In other words, the combination of drugs did not increase the incidence of adverse reactions.*

Conclusions: *Alteplase intravenous thrombolysis combined with butylphthalide in the treatment of severe cerebral infarction is safe, and may significantly improve patient's neurological function and quality of life without adverse reactions.*

Key words: *severe cerebral infarction, alteplase, intravenous thrombolysis, butylphthalide, therapeutic effect.*

Introduction

As a kind of cerebrovascular disease, severe cerebral infarction is characterized by high incidence, disability, and mortality rates. It is a common cerebrovascular disease that involves ischemia and hypoxic necrosis of the brain tissue caused by a sudden blood circulation disorder. Severe cerebral infarction has a rapid onset and rapid disease progression, showing high disability and mortality rates [16].

Severe cerebral infarction lesions comprise central necrosis and a peripheral cerebral ischemic penumbra.

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Due to the presence of collateral circulation, the ischemic penumbra can have a large number of surviving neurons [11,20]. With the increase of ischemic time and severity, the core enlarges, and the penumbra decreases. Studies have shown that due to the sharp decrease in blood supply, the reserve capacity of brain cells is reduced, and acidosis is prone to cause inflammatory reactions and a large number of free radicals, causing brain cell damage [12,15,19].

Recently, alteplase intravenous thrombolysis therapy has been widely used in the treatment of severe cerebral infarction [4,9]. In addition, butylphthalide can promote increased blood supply to the ischemic area, stimulate the establishment of collateral circulation, improve micro-circulation, effectively protect mitochondria [5], improve brain energy metabolism, inhibit free radicals in the body, and promote oxidase activity and infarction [6]. However, the effectiveness of alteplase intravenous thrombolysis combined with butylphthalide for treating acute severe cerebral infarction is rarely reported.

In this study, we investigated the effectiveness of intravenous thrombolysis with alteplase combined with butylphthalide in patients with severe cerebral infarction. Specific conditions are reported below.

Material and methods

Subjects

From February 2018 to March 2019, patients who suffered from severe cerebral infarction in the Rongcheng People's Hospital were recruited and randomly divided into two groups according to a random number table, i.e., an alteplase intravenous thrombolysis treatment group and alteplase intravenous thrombolysis combined with butylphthalide treatment group. The specific method was as follows: First, 100 patients with acute severe cerebral infarction were numbered from 1 to 100. Then, starting from any row or column in the random number table, three digits were read as a random number and entered; next, all selected random numbers were sequenced from small to large (random numbers with the same number were numbered in the first order). We specified that serial numbers from 1 to 50 were included into the alteplase intravenous thrombosis group, and that serial numbers from 51 to 100 consisted of the alteplase intravenous thrombosis combined with butylphthalide group. This study was conducted in accordance with the Declaration of Helsinki and approved by ethics committee of the Rongcheng People's Hospital (No. 2018-01-A). All participants provided signed informed consent forms for involvement in the study.

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients who were diagnosed with severe cerebral infarction according to Chinese guidelines for the diagnosis and treatment of acute ischemic stroke (2018), which were approved by the Chinese Society of Neurology and Chinese Stroke Society; 2) Patients aged 18 years and older; 3) Patients who provided signed informed consent. Exclusion criteria: 1) Patients who had severe coagulation dysfunction or a previous history of intra-cranial hemorrhage; 2) Patients, whose history details and clinical information were not clear; and 3) Patients who had severe dysfunction of the heart and other vital organs, or those with a malignant tumor.

Methods

In the alteplase intravenous thrombolysis group, patients were treated with alteplase intravenous thrombolysis. Once indications for intravenous thrombolysis were clear, the patients were given alteplase thrombolysis at a dose of 0.9 mg/kg. The maximum dose was less than or equal to 90 mg. After 100 ml of alteplase was mixed with a 9 g/l sodium chloride injection, 10% of the total dose was injected intravenously within two minutes, and the remaining 90% was delivered *via* an infusion pump within one hour (intravenous drip treatment). The administration of antiplatelet aggregation and anticoagulant drugs within 24 hours after intravenous thrombolysis was avoided.

In the alteplase intravenous thrombolysis combined with butylphthalide group, 25 mg of butylphthalide was injected intravenously over 50+ minutes, twice a day. The interval between the two administrations was not less than six hours, and the treatment continued for two weeks.

Main indicators

In this study, primary indicators included the efficacy of treatment methods, National Institutes of Health Stroke Scale (NIHSS) scores of the patients on the first, seventh, and fourteenth days after the different treatments, quality of life of the patients evaluated using Barthel scale before and after treatment, and the incidence of adverse reactions.

The following observations were noted accordingly:

- markedly effective: Symptoms and signs of acute severe cerebral infarction essentially disappeared, and NIHSS score improved by more than 90%;
- markedly effective: NIHSS score improved by more than 45%;
- markedly ineffective: Neither markedly effective nor effective scores were achieved.

The total effective rate equaled the sum of markedly effective and effective percentages [14].

Statistical analysis

SPSS Statistics v. 24.0 (IBM, Chicago, USA) software program was applied to conduct statistical analysis. Continuous variables of normal distribution were expressed as mean ± standard deviation, continuous variables of non-normal distribution were expressed as median (interquartile range), and categorical variables were expressed as frequency (percentage [%]). For two comparisons, each value was compared by a *t*-test when each datum conformed to normal distribution; non-normally distributed continuous data were compared using non-parametric tests. Counting data were tested with chi-square test. A value of $p < 0.05$ was considered statistically significant.

Results

General characteristics of participants

A retrospective analysis was performed, and 100 patients with acute cerebral infarction treated in the Rongcheng People's Hospital from February 2018 to March 2019 were randomly divided into two groups, with 50 cases in each group. There was no significant difference in baseline information between the two groups, as shown in Table I.

Effectiveness in the two groups

As shown in Table II, the total effective rate in the alteplase intravenous thrombolysis group was 80% (40 cases). Of note, the total effective rate in the alteplase intravenous thrombolysis combined with butylphthalide group was 100% (50 cases). The total effective rate in the latter was significantly higher compared with that in the former ($p < 0.05$).

Quality of life between the two groups

As shown in Table III, before treatment, the quality of life of the patients in the two groups was similar ($p > 0.05$). Following treatment, the quality of life of the alteplase intravenous thrombolysis combined with butylphthalide group was significantly better compared with that of the alteplase intravenous thrombolysis group ($p < 0.05$).

Table I. Comparative analysis of general information between experimental group and control group

Group	Age	Male, *n* (%)	Weight (kg)	Course of disease (h)	Infarct range (cm^3)	NIHSS score
Alteplase intravenous thrombolysis group	62.13 ±5.46	26 (52)	55.21 ±0.35	2.13 ±0.19	6.18 ±1.46	19.13 ±6.54
Alteplase intravenous thrombolysis combined butylphthalide group	63.22 ±4.06	25 (50)	55.23 ±0.31	2.09 ±0.21	6.16 ±1.51	18.69 ±7.21
t/χ^2	0.79	0.52	0.27	0.43	0.63	0.64
p-value	0.51	0.48	0.65	0.72	0.68	0.52

Table II. Comparison of therapeutic effects between two groups [cases (%)]

Group	Number of cases	Markedly effective	Effective	Invalid	Total effective rate
Alteplase intravenous thrombolysis group	50	20	20	10	40 (80.00)
Alteplase intravenous thrombolysis combined butylphthalide group	50	40	10	0	50 (100.00)
χ^2					6.968
p-value					0.025

Table III. Comparison of quality of life before and after treatment (`x ±s, points)

Group	Number of cases	Before treatment	After treatment
Alteplase intravenous thrombolysis group	50	64.20 ±2.27	80.20 ±2.11
Alteplase intravenous thrombolysis combined with butylphthalide group	50	64.11 ±2.44	97.26 ±3.23
t		0.821	6.214
p-value		0.014	0.000

Table IV. Comparison of NIHSS scores between two groups on 1 day, 7 days, and 14 days after treatment (points)

Group	Number of cases	Before treatment	1 day after treatment	7 days after treatment	14 days after treatment
Alteplase intravenous thrombolysis group	50	14.21 ±2.13	10.24 ±2.12	9.22 ±2.21	6.01 ±2.12
Alteplase intravenous thrombolysis combined with butylphthalide group	50	14.13 ±2.22	8.25 ±1.23	7.11 ±1.44	5.03 ±1.21
t		0.144	6.821	6.245	6.267
p-value		0.746	0.000	0.000	0.000

Table V. Comparison of incidence of adverse reactions between two groups [cases (%)]

Group	Number of cases	Bleeding gums	Subcutaneous ecchymosis	Gastrointestinal bleeding	Other	Incidence
Alteplase intravenous thrombolysis group	50	1	1	0	1	3 (6.00)
Alteplase intravenous thrombolysis combined with butylphthalide group	50	1	1	0	0	2 (4.00)
χ^2						0.134
p-value						0.721

National Institute of Health Stroke Scale of the patients

As listed in Table IV, before treatment, the NIHSS scores of the patients in both the groups were similar ($p > 0.05$). After treatment, in the alteplase intravenous thrombolysis combined with butylphthalide group, NIHSS scores of the patients on 1, 7, and 14 days after treatment were 8.25 ±1.23, 7.11 ±1.44, and 5.03 ±1.21, respectively. In the alteplase intravenous thrombolysis group, NIHSS scores of the patients on 1, 7, and 14 days after treatment were 10.24 ±2.12, 9.22 ±2.21, and 6.01 ±2.12, respectively. Compared with the latter group, after treatment, NIHSS scores of the patients on first, fourth, and fourteenth days in the former group were significantly decreased ($p < 0.05$).

Incidence of adverse reactions between the two groups

As shown in Table V, the incidence of adverse reactions in the alteplase intravenous thrombolysis group was 15% (three cases). The incidence of adverse reactions in the intravenous thrombolysis combined with butylphthalide group was 10% (two cases). Accordingly, the incidence of adverse reactions in the latter group was similar to that in the former ($p > 0.05$).

Discussion

In the case of ischemia and reperfusion, various inflammatory factors can trigger local inflammatory reactions and aggravate micro-circulation dysfunction. Early thrombolytic therapy can re-canalize occluded blood vessels, restore blood flow, save ischemic penumbra brain tissue, and effectively improve patient's prognosis. A third-generation thrombolytic drug, alteplase, is an endogenous enzyme [3,21]. Although it is difficult to activate plasminogen without fibrin, alteplase can easily activate plasminogen in the thrombus. It is converted into plasmin to dissolve the thrombus, and subsequently exerts a strong local thrombolytic effect [10]. Intravenous thrombolysis has been widely applied in clinical settings; however, the application is greatly limited due to the short time window (within three hours) [2]. Therefore, it is of great clinical value to optimize intravenous thrombolysis in the treatment of severe cerebral infarction. Of note, combination therapy is often a good option. We propose that alteplase intravenous thrombolysis combined with butylphthalide is an effective treatment for severe cerebral infarction.

Butylphthalide is a novel anti-cerebral ischemia drug that has been shown to interfere with pathophysiological development of cerebral ischemia by scavenging free radicals and other ways [5]. Butylphthalide can also significantly improve neurological functions of patients with brain injury [17], improve micro-circulation and blood flow in the ischemic brain area, increase the number of capillaries in the blood area, reduce the area of ischemic infarction, relieve brain edema, and inhibit nerve cell decay among other effects [6,18,22]. Numerous studies have proven that butylphthalide has a good therapeutic effect on cerebral infarction, providing good safety [1,13,17]. It was approved to be mar-

keted in 2004, and butylphthalide injections began to be produced in 2009.

The present study showed that the NIHSS score of the combined group was lower than that of the alteplase group after treatment, indicating that combined butylphthalide treatment can effectively improve patients' central nerve damage. This is consistent with research conclusions of Chen *et al*. [7], Bracard *et al*. [4], and Emberson *et al*. [8]. Previous research results suggested that the possible mechanism of this effect is that butylphthalide can inhibit the formation of free radicals and improve the activity of oxidase, thus reducing the degree of neurological impairment. In addition, the quality of life of the combined treatment group was significantly better than that of the alteplase group. This may be related to the improvement of the patients' damaged central nervous system, which controls the limbs of the body. When the central nervous system was relieved, the patients' symptoms were relatively reduced, and their quality of life was improved. After treatment, the total effective rate of the combined group was higher than that of the alteplase group, indicating that the combined alteplase and butylphthalide treatment had a better curative effect, which may be related to the fact that butylphthalide can directly improve local symptoms in the brain by reducing the area of local infarction and increasing the number of blood capillaries [3,10,21]. At the same time, there was no significant difference in the incidence of side effects between the combination group and the alteplase group, indicating that the combination of butylphthalide therapy did not increase the risk, and that the combination is safe and effective. This is consistent with research results of Qin and Zhu [14], Hu *et al*. [10], and others. However, considering the limited sample size and short observation time, we will conduct a comprehensive multi-center study with a larger sample size and longer follow-up time in the future to explore the safety and long-term efficacy of the drugs.

Cerebral infarction is a disease with a complex pathogenesis, and many pathways are involved in the course of pathogenesis. Alteplase combined with butylphthalide is a multi-target treatment that can certainly achieve better efficacy under the condition of ensuring drug safety. This retrospective study provided the latest supporting evidence for the use of alteplase combined with butylphthalide in the treatment of acute cerebral infarction.

The present study included several limitations. First, the administration methods of the groups were different, so this was a randomized controlled trial without a blind method. To avoid the influence of subjective factors on the evaluation of the results, bias in clinical trials should be reduced as much as possible, and the rationality and scientificity of clinical trials should be improved. Our follow-up investigation will pay attention to adopting a blind method. Second, the study was a single-center trial; multi-center trials should be conducted as part of future research in this regard. Third, the sample size of this study was very limited; a larger trial with additional participants should be conducted in the future. Lastly, the clinical follow-up was short, although it was necessary to observe long-term clinical prognoses. In general, only patients within six hours of onset were analyzed. In this respect, we are taking a variety of countermeasures to make up for this limitation, such as including more patients, increasing treatment data of patients in different time windows, and prolonging follow-up time.

Conclusions

For patients with severe cerebral infarction, alteplase intravenous thrombolysis combined with butylphthalide has a higher efficacy than alteplase intravenous thrombolysis alone, significantly improving patients' neurological function and quality of life without increasing the incidence of adverse reactions. The findings of this study provide new ideas for the treatment of these patients.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by ethics committee of the Rongcheng People's Hospital. All participants provided signed informed consent forms for involvement in the study.

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Disclosure

The authors report no conflict of interest.

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