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Original Article

Clinical curative effect analysis of combination therapy with urinary kallidinogenase, butylphthalide, and edaravone on acute ischemic stroke

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Abstract: Objective: The aim of this study was to investigate the efficacy of combination therapy with urinary kallidinogenase, butylphthalide, and edaravone on cerebrovascular reserve (CVR) function and nervous system function of patients with acute ischemic stroke. Methods: A total of 84 patients with acute ischemic stroke, admitted by the Neurology Department of Daqing Oilfield General Hospital, from August 2015 to April 2016, were enrolled. They were randomly divided into an observation group and a control group depending on sequence of hospitalization, each with 42 patients. The control group was given conventional therapy including anticoagulation, lipid-lowering, and neurotrophic support. The observation group was given combination therapy with urinary kallidinogenase, butylphthalide, and edaravone in addition to standard treatment. After the 2-week treatment, clinical effects, cerebrovascular reserve function, cerebral hemodynamic indices, and breath-holding index (BHI) were evaluated. Neurological function defect and side effects of patients, before and after treatment, were evaluated with National Institute of Health stroke scale (NIHSS) and Modified Barthel Index (MBI). Results: Overall response rate (ORR) of the observation group (95.2%) was higher than the control group (80.9%; $P<0.05$). Peak velocity, mean velocity, CVR, and BHI of the observation group were increased. NIHSS scores of the two groups decreased remarkably, compared to before treatment, but scores of the observation group decreased more than the control group, suggesting that the results had statistical significance. Differences of the two groups in rate of adverse reactions had no statistical significance ($P>0.05$). Conclusion: Combination therapy with urinary kallidinogenase, butylphthalide, and edaravone can effectively improve brain blood circulation, enhance the capability of the organism to stabilize cerebral circulation reserve, improve neurological function of patients with acute ischemic stroke, and significantly improve clinical efficacy, without increasing the rate of adverse effects.

Keywords: Ischemic stroke, urinary kallidinogenase, butylphthalide, edaravone, clinical effect

Introduction

Strokes are the world's second leading cause of death or disability. About 85% of strokes are ischemic strokes [1, 2]. Acute ischemic stroke is the hypoxia-ischemia of brain tissues caused by blood vessel thrombosis or blood vessel occlusion, thus, leading to dysfunction. Incidence of this disease is highest among the elderly. Actively optimizing stepwise prevention of ischemic strokes, reducing complications, and promoting recovery of neurological functions should be the goal of ischemic stroke therapies [3]. Current treatment goals are to facilitate recanalization of blood vessels with lesions, rescue ischemic brain tissues, and provide energy to satisfy the energy demands of cells in ischemic areas to buy time for further treatment [4].

The main therapies for ischemic stroke include medication and intervention. Intervention is active in recanalization of blood vessels [5, 6]. One random trial demonstrated that the clinical effects of intervention are not better than that of medication. Therefore, medication remains the main choice for therapy [7]. After several years of research, medication treatment of ischemic stroke has gradually changed from single-drug therapy to drug combination

Table 1. Comparison of general data between the two groups

Item	Observation group (n=42)	Control group (n=42)	t/χ^2	P
Age (years old)	72.3±10.8	71.8±9.9	0.221	0.826
Gender (male/female)	17/25	21/21	0.789	0.380
Smoking history	6	9	0.816	0.366
Diabetes history	11	15	0.891	0.345
Hypertension	19	20	0.048	0.826

Table 2. Comparison of cerebral blood supply before and after treatment between the two groups

	Observation group	Control group	t	P
Peak velocity				
Before treatment	55.3±2.1	54.9±2.5	0.794	0.430
After treatment	61.2±5.9	70.3±7.6	6.130	<0.001
t	6.106	12.474		
P	<0.001	<0.001		
Mean velocity				
Before treatment	79.8±1.6	80.2±1.2	1.296	0.199
After treatment	83.1±1.9	86.5±1.5	9.102	<0.001
t	8.610	21.255		
P	<0.001	<0.001		
Pulsatility index				
Before treatment	0.95±0.16	0.93±0.17	0.555	0.580
After treatment	0.83±0.19	0.73±0.12	2.288	0.025
t	3.131	4.797		
P	0.002	<0.001		

therapy [8]. Current research is limited to single-drug therapies or two-drug combination therapies. In this study, 84 patients, suffering from acute ischemic stroke, admitted by the Neurology Department to Daqing Oilfield General Hospital, were selected as subjects. The aim of this study was to evaluate the effectiveness and safety of the combination of urinary kallidinogenase, butylphthalide, and edaravone regarding clinical effects and adverse reactions.

Materials and methods

Subjects

A total of 84 patients with acute ischemic stroke, admitted by the Neurology Department of Daqing Oilfield General Hospital, from August 2015 to April 2016, were selected as subjects for this prospective study. They were randomly divided into an observation group and control group, depending on sequence of hospitalization, each with 42 patients.

Inclusion criteria: 1) patient age was above 20 and below 75; 2) patient diagnosed with acute cerebral infarction by brain CT and magnetic resonance imaging, inaccordwith diagnosis criteria revised by the 4th National Cerebrovascular Disease Academic Conference, while the possibility of cerebral hemorrhage was excluded; 3) first stroke the patient had experienced or patient had recovered from a previous stroke with no sequela remaining from the previous lacunar infarction; and 4) patient had not suffered from any obvious symptoms of neurological function defects at the time of onset of the illness.

Exclusion criteria: 1) patients suffering from functional insufficiency of any other major organ; 2) patients allergic to urinary kallidinogenase, butylphthalide, or edaravone; 3) patients carrying a birth defect that could affect research results; 4) patients suffering from a hematological disease or coagulation function insufficiency; and 5) patients with history of gastrointestinal ulcer and hemorrhage.

Both groups of patients provided informed consent. This study was approved by the Ethics Committee of Daqing Oilfield General Hospital.

Methods

After hospitalization, both groups of patients were given conventional initial therapies (including aspirin & clopidogrel double-antibody, blood lipid control, and blood glucose regulation) for stabilization of their internal environments. The following intravenous drugs were used: mannitol conventionally administered to relieve edema, adenosine triphosphate, and acetyl coenzyme A to supplement energy.

In addition, the observation group was administered urinary kallidinogenase (0.15 PNA U, dissolved in 100 mL of normal saline) within 30-60

Table 3. Comparison of NIHSS scores between the two groups

Group	NIHSS score		t	P
	Before treatment	After treatment		
Control group	9.18±0.99	6.12±1.40	11.566	<0.001
Observation group	9.25±1.10	3.77±1.20	21.816	<0.001
t	0.070	8.259		
P	0.760	<0.001		

Note: NIHSS, National Institutes of Health Stroke Scale.

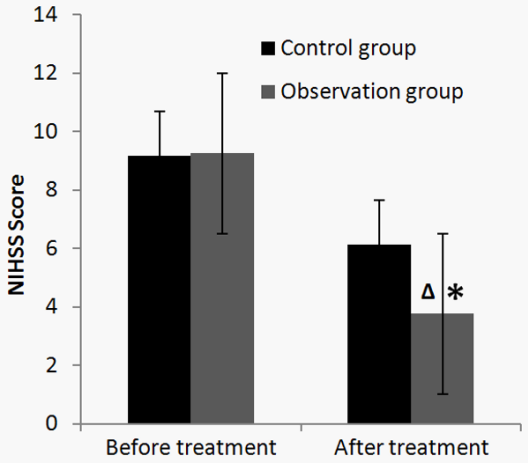

Figure 1. Comparison of NIHSS scores between the two groups. Patients in the control group (n=42) were treated with conventional treatment, and the group (n=42) were treated with the combined treatment regimen for 2 weeks. Comparison of the NIHSS scores between the two groups before treatment, P<0.001; comparisonof the NIHSS scores between the two groups after treatment, *P<0.001.

minutes, once a day; Edaravone (30 mg/d) within 30 minutes, twice a day; Butylphthalide and sodium chloride injection (containing 25 mg of butylphthalide), twice a day, 100 mL each time.

The control group was administered a normal amount saline equal to that of urinary kallidinogenase, butylphthalide, and edaravone. Both groups were treated for 2 weeks.

Outcome measures

Symptoms of neurological function defects: National Institutes of Health Stroke Scale (NHISS) was used to evaluate the improvement of neurological function of patients after 2 weeks of treatment. Evaluation criteria: Almost healed, patient NHISS score decreased by ≥90.0%; Apparently effective, patient NHISS score decreased by 45.0%-90.0% (including 45%); Effective, patient NHISS score decreased by 18.0%-45.0%; Ineffective, patient NHISS score decreased by ≤18.0% or increased but the patient cannot live without the help of others. In the first three cases, treatment was clinically effective. Clinical efficacy rate = number of case (almost healed + apparently effective + effective)/total number of cases * 100%.

Cerebral hemodynamic evaluation: The same doctor from the Ultrasonic Department evaluated hemodynamic changes of both groups, before and after treatment, recording cerebral hemodynamic indices (peak velocity (Vp), mean velocity (Vm), and pulsatility index (PI)) and measuring mean flow velocity (MFV) of bilateral middle cerebral arteries of patients when resting or after holding their breath. Cerebrovascular reserve (CVR) and breath holding index (BHI) were also calculated. CVR = difference between MFV after breath holding and base MFV/base MFV * 100%; BHI = (difference between MFV after breath-holding and base MFV/base MFV * 100)/breath holding time.

Adverse reactions record: Rates of adverse reactions (tinnitus, rash, ecchymosis, etc.) of the patients were recorded.

Statistical analysis

SPSS20.0 statistical software was used for analysis. Normal measurement data of both groups are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent, normal, and equal variance-assumed data were compared within a group by paired-samples t-tests and between two groups by independent-sample t-tests. Enumeration data were compared by Chi-square test. P<0.05 signified that differences were statistically significant.

Results

Comparison of general data between the two groups

Results showed that the two groups had no statistical differences in general data regard-

Table 4. Clinical efficacy of the two groups (case)

Group	Therapeutic effect				Clinical efficacy rate
	Almost healed	Apparently effective	Effective	Ineffective	
Control group	12	10	12	8	80.9%
Observation group	22	15	5	2	95.2%
t			10.383		4.086
P			0.016		0.043

ing age, gender, smoking history, diabetes history, and hypertension (all P>0.05). The two groups were comparable as shown in **Table 1**.

Comparison of cerebral hemodynamic indices before and after treatment between the two groups

Differences between the two groups in cerebral hemodynamic indices, before treatment, had no statistical significance (all P>0.05). After treatment, Vp and Vm of the two groups increased while PI decreased, remarkably, compared with those before treatment. Amplitude of change of the observation group was larger than that of the control group. The above differences had statistical significance (all P<0.05), as shown in **Table 2**.

Comparison of NIHSS scores between the two groups

Differences between the two groups in NIHSS scores, before treatment, had no statistical significance (P>0.05). After 2 weeks of treatment, NIHSS scores of two groups decreased evidently (both P<0.001). NIHSS scores of the observation group, after treatment, were obviously lower than those of the control group (P<0.001) as shown in **Table 3** and **Figure 1**.

Clinical efficacy of the two groups

The clinical efficacy rate of the observation group was 95.2%, higher than that of the control group (80.9%; P<0.05) as shown in **Table 4**.

Comparion of CVR and BHI between the two groups

Results showed that the two groups had no statistical difference in CVR and BHI, before treatment (both P>0.05), while conditions of both groups of patients greatly improved after treatment (both P<0.001). CVR and BHI of the observation group were significantly better than those of the control group (both P<0.001) as shown in **Table 5**.

Adverse reactions of the two groups

A total of 3 patients in the observation group had tinnitus while 1 had ecchymosis. Two patients in the control group had rashes and 1 had ecchymosis. There were no statistical differences in adverse reaction rates between the two groups (χ^2=0.288, P=0.866).

Discussion

Acute ischemic strokes are a major global health issue. Ischemic strokes cause 10% of all deaths, annually. It can also cause permanent nervous system injuries [9, 10]. Unfortunately, none of the currently existing research has made a breakthrough, as research is limited to animal tests in cellular areas. Clinically, single-drug therapies cannot achieve ideal effects. Current treatment tends to use comprehensive therapies for acute ischemic stroke, reporting positive clinical effects [11].

CVR means that the organism under stress activates its regulatory function to cause compensatory contraction or expansion of cerebral arterioles and capillaries, hence, realizing the redistribution of cerebral vascular flow and stability of cerebral blood flow. CVR has been closely associated with prognosis of acute ischemic stroke [12]. Therefore, improving CVR has a positive effect on patients with acute ischemic stroke. Some studies, through animal experimentation, have revealed that urinary kallidinogenase could selectively expand arterioles and promote generation of blood vessels in ischemic tissues. It could catalyze kininogens, thereby causing the organism to have the above biological effects [13, 14]. Results of the present research showed that there was more improvement regarding cerebral vascular hemodynamics in the combination therapy group than in the control group. In the present research plan, it was noted that urinary kallidinogenase could improve CVR, consistent with previous research results [15].

Edaravone can protect cerebral nerve cells, inhibiting apoptosis by removing free radicals generated by brain cells due to ischemia-hypox-

Table 5. Comparion of CVR and BHI between the two groups

Group	CVR (%)		t	P	BHI		t	P
	Before treatment	After treatment			Before treatment	After treatment		
Control group	18.9±1.4	24.7±3.3	10.486	<0.001	0.79±0.16	1.21±0.19	10.958	<0.001
Observation group	19.3±2.9	31.9±4.4	15.496	<0.001	0.81±0.13	1.56±0.15	24.487	<0.001
t	0.805	8.484			0.629	9.370		
P	0.423	<0.001			0.531	<0.001		

Note: CVR, cerebrovascular reserve; BHI, breath-holding index.

ia and suppressing the oxidative stress response caused by cerebral ischemia. It can also reduce reperfusion injury of brain tissues [16-18]. This study found that additional use of urinary kallidinogenase could effectively increase cerebral blood flow perfusion and promote the increase of CVR and BHI.

One previous study has proven that butylphthalide can suppress several pathological links of pathophysiological processes of brain injuries arising from ischemic strokes [19]. The operation mechanism is possibly through inhibiting the release of glutamic acid by reducing the arachidonic acid content, *in vivo*, and increasing levels of NO released by vascular endothelial cells and prostacyclins in brain tissues. This process could achieve the ultimate goal of suppressing nerve injuries, improving brain tissue circulation, and symptoms of neurological function defects [20]. This study demonstrated that NIHSS scores of the observation group improved and the clinical effects were significantly superior to that of the control group, proving the clinical effects of butylphthalide in combination therapy.

Compared with the control group, combination of urinary kallidinogenase, butylphthalide, and edaravone did not increase adverse reaction rates of the patients. These results support the safety of this combination therapy regimen.

However, this study was a 2-week research trial with a relatively small sample size. Improvements regarding clinical symptoms of ischemic stroke and effects on prognosis must be further demonstrated by multi-center large-scale clinical trials.

In conclusion, patients suffering from ischemic stroke were treated with urinary kallidinogenase, butylphthalide, and edaravone and observed. This combination therapy can effectively improve blood circulation in the brains of patients with acute ischemic stroke, enhance the capability of the organism to stabilize cerebral circulation reserve, and improve neurological function, indicating that this option is safe and effective.

Disclosure of conflict of interest

None.

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