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Original Research Article

Effect of intravenous thrombolysis with butylphthalide, edaravone and recombinant tissue plasminogen activator (rt-PA) on serum inflammatory factors in patients with ischemic stroke

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Abstract

Purpose: *To study the impact of edaravone in combination with edaravone and recombinant tissue plasminogen activator (rt-PA) intravenous thrombolysis on serum inflammatory factors in ischemic stroke subjects.*
Methods: *Eighty ischemic stroke patients in the First Affiliated Hospital of Xi'an Medical University, Xi'an, China were randomly assigned to study and control cohorts, each with 40 subjects. Patients in control cohort were administered edaravone and rt-PA intravenous thrombolysis. The study cohort received butylphthalide in combination with edaravone and rt-PA intravenous thrombolysis. Treatment effectiveness/efficacy, neurological function, self-care ability, inflammatory indicator levels, and blood cell levels were compared between the 2 cohorts.*
Results: *Efficacy was significantly better in the study cohort than in the control cohort ($p < 0.05$). After treatment, NIHSS score was significantly lower in the study cohort than in control cohort, while ADL score was significantly higher in the study cohort ($p < 0.05$). After medication, CRP level was decreased significantly in both cohorts, but was significantly lower level in the study cohort ($p < 0.05$). Treatment led to significant reductions in white blood cell count, neutrophil count, and NLR ratio in the study cohort, relative to the control cohort ($p < 0.05$).*
Conclusion: *The use of butylphthalide in combination with edaravone and rt-PA intravenous thrombolysis produces significant and beneficial effects on ischemic stroke subjects by regulating abnormal levels of inflammatory cells, improving coagulation status and decreasing inflammation. Moreover, it ameliorates neurological defects and improves activities of daily living. There is, however, a need to determine the mechanisms of action of this combination therapy and the influence of other co-founding factors on the activities of the combination therapy.*

Keywords: *Butylphthalide, Edaravone, Recombinant tissue plasminogen activator (rt-PA), Intravenous thrombolysis, Ischemic stroke, Inflammatory factors*

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INTRODUCTION

Acute ischemic stroke is a disease arising from the obstruction of cerebral arteries due to cerebral arteriosclerosis or other reasons, leading to insufficient perfusion in the blood supply area, thereby resulting in ischemic necrosis of brain tissue. It is a highly prevalent

cerebrovascular disease with high mortality, high disability, and low cure rate, and it poses a severe threat to the safety of lives of patients [1]. Ischemic stroke occurs rapidly and often leaves sequelae such as hemiplegia, facial droop, and speech disorder after treatment [2]. Currently, there is no unified standard treatment for ischemic stroke in practice. The main strategies used are thrombolysis, anticoagulation, and other conventional Western symptomatic treatments, and rehabilitation training [3]. Intravenous thrombolysis with rt-PA and intravascular treatment are effective treatments for acute ischemic stroke [4].

Edaravone and *Yimian* are new types of cerebral cell protection drugs composed of edaravone and borneol, respectively. Studies have shown that these drugs have anti-inflammatory and antioxidant potential which can prevent brain damage from ischemic stroke [5]. Butylphthalide is a new drug developed from celery by the Institute of Materia Medica, Chinese Academy of Medical Sciences. Moreover, the technology of artificial synthesis of butylphthalide has been developed. Butylphthalide acts by improving local cerebral circulation, reducing brain edema, promoting nerve repair, and promoting vascular regeneration in the lesion area [6]. In this study, the effects of butylphthalide in combination with edaravone and rt-PA intravenous thrombolysis on serum inflammatory factors in ischemic stroke subjects to generate background data for the selection of treatment methods for ischemic stroke.

METHODS

General information on patients

Eighty (80) patients with ischemic stroke who received treatment at First Affiliated Hospital of Xi'an Medical University, Xi'an, China from January 2022 to December 2023 were assigned to study and control cohorts (n = 40 per group). The control cohort comprised 22 males and 18 females aged 40 - 82 years (mean age = 58.63 ± 9.34 years), with 22 cases of ischemic stroke in the basal ganglia area, 15 cases in the thalamus, and 9 cases close to the lateral ventricle. In the study cohort, there were 23 males and 17 females aged 42 - 80 years, with an average age of 57.48 ± 8.86 years. The study group had 23 cases of ischemic stroke in the basal ganglia area, 16 cases in the thalamus, and 7 cases next to the lateral ventricle. Both cohorts were comparable in sex, age, infarct location and other biodata. This study was approved by the ethics committee of the First Affiliated Hospital of Xi'an Medical University, Xi'an, China (approval no. xmu2021006). All subjects voluntarily participated and signed informed consent forms, or had them signed by their family members.

Inclusion criteria

Patients who satisfied the parameters for diagnosis of ischemic stroke [7]; those who had good vital signs, and who sought medical attention within 4 h following the appearance of symptoms; and subjects with no abnormalities in coagulation function, were included in the study.

Exclusion criteria

The excluded patients were those with malignant tumors and severely dysfunctional organs; subjects who were allergic to the drugs used in this study; patients who had undergone craniotomy surgery or previous intervention or thrombolysis therapy; and patients with severe illnesses related to immunity, nervous system or blood.

Treatments

Patients in the control cohort were given edaravone, dexamethasone and rt-PA intravenous thrombolysis. The rt-PA was administered at a dose of 0.9 mg/kg (the total intake did not exceed 90 mg), with 10 % given as an intravenous bolus, while the remainder was given as a continuous intravenous infusion over a 1-h period. During the entire process of intravenous thrombolysis, the condition of the patient was continuously monitored. If any severe adverse reactions occurred, the thrombolysis was stopped immediately.

After thrombolysis, basic treatment was given. After 24 h, a brain CT scan was repeated to see if cerebral hemorrhage was present, and then conventional antiplatelet or anticoagulation therapy was started. Edaravone and dexamethasone (Simcere Pharmaceutical Group Limited; China Medical Products approval no. H20200007; packaging specification: 10 mg edaravone/5 mL; 2.5 mg dexamethasone/5 mL) were given intravenously, each in a volume of 15 mL (i.e., 30 mg edaravone and 7.5 mg dexamethasone), twice daily. Prior to use, each drug was diluted in 100 mL of normal saline and given intravenously over a 30-min period. The treatment was continued for 14 days, starting within 48 h of onset.

Patients in the study cohort were given butylphthalide, edaravone and rt-PA intravenous thrombolysis, and the treatments with edaravone, rt-PA and rt-PA were the same as those of the

control group. Butylphthalide and sodium chloride injections (Shijiazhuang Pharmaceutical Group Enbipure Pharmaceutical Company Ltd.; Chinese Pharm. approval no. H20100041; specification: 25 mg butylphthalide/100 mL; 0.9 mg sodium chloride/100 mL) were given intravenously, twice daily, 25 mg at a time, for 14 days.

Evaluation of parameters/indices

Treatment efficacy

Efficacy in patients was evaluated using the GCS scoring scale [7]. It was categorized as *excellent* (5 points), i.e., the subject was able to lead a normal life, with mild neurological impairment, and good recovery; *good* (4 points), i.e., mild hemiplegia and mild disabilities, but the patient was able to do self-care in daily life; *fair* (3 points), i.e., relatively clear consciousness, difficulty in taking care of oneself in daily life, and severe disability; and *poor* (2 points), i.e., vegetative state and no consciousness, although with heartbeat and breathing. Treatment effectiveness was determined by summing up the number of patients in the *excellent* and *good* categories.

Neurological function and self-care ability

The National Institutes of Health Stroke Scale (NIHSS) was used to assess the neurological impairment of patients [8,9]. This scale comprised 11 dimensions. It had scores ranging from 0 to 42 points, with higher scores indicating more severe impairment [5]. Self-care capacity was measured with the Activities of Daily Living Scale (ADL), with scores ranging from 0 to 100. Better self-care ability was indicated by higher scores [6].

Inflammatory indicators

Following overnight fast, 5 mL of blood was drawn from the vein of each subject, and the supernatant (serum) obtained when the sample was centrifuged at 3000 rpm for 15 min, was refrigerated prior to subsequent use. Enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of C-reactive protein (CRP) in patients. The instrument used for the ELISA was a Bio-Tek automatic microplate reader from the United States, at a wavelength of 450 nm. All the reagent kits were products of Shanghai Enzyme-linked Biol. Co. Ltd., and were operated in line with the protocols specified in the reagent kits.

Blood cell levels

The concentrations of leukocytes, polymorphonuclear leukocytes and lymphocytes were determined using the XE5000 automatic blood analyzer (Sysmex Corporation, Japan), and the neutrophil-to-lymphocyte ratio (NLR) was calculated.

Statistical analyses

The SPSS 20.0 was used for statistical analysis. Count data were compared using $\chi 2$ test. Measurement data are presented as mean ± standard deviation (SD), and *t*-test was used for comparison. Values of $p < 0.05$ were assumed to be indicative of statistically significant differences.

RESULTS

Treatment effectiveness/efficacy

Treatment effectiveness was significantly better in the study cohort than in the control cohort, as shown in Table 1.

Table 1: Treatment effectiveness in each cohort (n=40)

Group	Excellent	Good	Fair	Poor	Total efficacy
Study	23	11	4	2	34 (85.00)
Control	12	13	8	6	26 (66.67)
$\chi 2$					4.267
P-value					0.039

Effect of treatment on NIHSS and ADL scores

Pre-treatment NIHSS and ADL scores were comparable in the 2 cohorts. However, after treatment, NIHSS score was markedly lower in the study cohort and also lower than the control cohort score, while ADL score was markedly raised, relative to the value before treatment, and also higher than the control cohort score ($p < 0.05$; Table 2).

Concentrations of inflammatory indicators

Pre-treatment concentrations of inflammatory markers were comparable in the 2 cohorts. However, treatment markedly lowered CRP levels in both cohorts, with markedly lower values in the study cohort than in the control cohort ($p < 0.05$). These data are shown in Table 3.

Table 2: NIHSS and ADL Scores in both cohorts (points, mean ± SD, n = 40)

Group	ADL		NIHSS	
	Before	***After***	***Before***	***After***
Control	33.12±5.84	51.23±6.46*	22.12±3.87	13.52±2.47*
Study	32.52±5.42	63.52±7.73*	21.42±4.23	10.62±2.25*
t	0.511	-8.274	0.828	5.887
P-value	0.611	0.000	0.410	0.000

Note: *$P < 0.05$ vs pre-medication

Table 3: Levels of inflammatory indicators in the 2 cohorts (n=40)

Group	CRP (ng/mL)	
	Pre-medication	***Post-medication***
Study	252.41±37.58	171.38±23.14*
Control	251.82±38.10	215.42±29.85*
t	0.079	-8.327
P-value	0.937	0.000

Note: *$P < 0.05$ vs pre-treatment

Impact of treatment on blood cell counts

The counts of polymorphonuclear leukocytes, neutrophils, and NLR ratio were similar in both cohorts, before medication. However, counts of polymorphonuclear leukocytes, neutrophils, and NLR ratio were markedly lower in the study cohort than the corresponding counts before treatment and lower than the control cohort counts ($p < 0.05$), as shown in Table 4.

DISCUSSION

Ischemic stroke, the main type of cerebrovascular disease, is caused by the obstruction and rupture of cerebrovascular vessels, leading to a group of organic brain injuries due to cerebral tissue ischemia and hypoxia [10]. In recent years, with the intensification of the aging problem in China and the changes in living and dietary habits, the incidence of ischemic stroke has been rising yearly, a situation that endangers the lives and safety of Chinese people [11]. Studies have found that the mortality rate of patients with ischemic stroke within one month is 3.3 to 5.2 %, and every year, it is 11.4 to 15.4 % [12].

Currently, there is no effective radical treatment for ischemic stroke in practice. Most patients are treated with intravenous thrombolysis to re-canalize embolized arteries. However, due to strict time constraints, medical conditions, contraindications, indications, and other factors, only a small number of patients receive the most effective treatments [13]. Therefore, it is of clinical significance to actively seek other effective treatments for patients with ischemic stroke with a view to improving prognosis in patients. The rt-PA intravenously administered thrombolysis and endovascular treatment are effective treatments for severe ischemic stroke [4]. Edaravone and Yecanol are new types of cerebro-protective drugs composed of edaravone and borneol. Investigations have revealed that they have antioxidative and anti-inflammation impacts, and they prevent ischemic stroke-induced damage in brain tissue. Recently, butylphthalide was successfully developed as a cerebro-protective drug which may be synthesized artificially from celery. Studies have found that butylphthalide inhibits multiple links to cerebral ischemia-induced brain injury, thereby exerting a cerebro-protective effect [14].

In the present investigation, clinical efficacy was markedly better in the study cohort than in the control cohort. Before treatment, NIHSS and ADL scores were similar in the two groups of patients. However, after treatment, NIHSS score was lowered in the study cohort, relative to pre-treatment, and it was also less, when compared with the control cohort score, while ADL score was markedly increased, relative to that before treatment and the control cohort score. These data suggest that butylphthalide produced good effectiveness in the treatment of subjects with subarachnoid hemorrhage-induced cerebral vasospasm.

Table 4: Blood cell counts in the 2 cohorts (mean ± SD, n = 40)

Group	White blood cells ($\times 10^9$/L)		Neutrophils ($\times 10^9$/L)		NLR	
	Before	***After***	***Before***	***After***	***Before***	***After***
Study	9.54±1.30	8.12±1.20*	7.44±0.65	4.38±0.64*	4.32±1.34	2.52± 0.75*
Control	9.56±1.25	8.74±1.52*	7.60±0.57	5.62±0.56*	4.36±1.40	2.98± 0.72*
t	-0.493	-3.070	0.963	-5.201	-0.544	-6.693
P-value	0.623	0.003	0.338	0.000	0.588	0.000

Note: *$P < 0.05$ vs pre-medication

Several studies have confirmed that butylphthalide raised levels of prostacyclin and NO in vascular endothelium, thereby reducing calcium ion concentration and alleviating cerebral vasospasm. In addition, butylphthalide inhibited the downregulation of caveolin-1 expression and the upregulation of tight junction-related protein expression, thereby reducing brain edema and improving cerebral blood circulation [15]. Furthermore, butylphthalide reduced mitochondrial damage, improved cerebral microcirculation, promoted the growth of capillaries in ischemic areas, significantly increased blood flow in ischemic areas, and protected brain tissue and nerves [16].

Studies have found that inflammation is one of the important mechanisms that cause early neurologic damage associated with severe ischemic stroke [15]. Arterial obstruction causes changes in body hemodynamics, leading to cerebral tissue hypoxia in patients. On activation, microglia cells release inflammation-related factors (e.g., CRP), which in turn, enhance the expressions of adhesion factors, thereby promoting the passage of peripheral blood monocytes and macrophages through the blood-brain barricade, and releasing pro-inflammatory mediators (e.g., IL-6), resulting in exacerbation of nerve and tissue damage [16]. Indeed, CRP is a pro-inflammatory factor that exacerbates local inflammation in brain tissue and nerve tissue damage [17]. In the present investigation, it was found that CRP level in the study cohort after treatment was markedly lower than the value before treatment, and also less than the control cohort value. This shows that the use of edaravone, butylphthalide and rt-PA intravenous thrombolysis reduced inflammation in stroke patients.

Neutrophils are key cells in the inflammatory response, and increases in their levels indicate increases in local or systemic inflammation in patients. Studies have found that neutrophils reach the site of cerebral infarction within minutes after the onset of ischemic stroke. Neutrophils not only form platelet-neutrophil aggregates with platelets and induce inflammatory factors to reach the ischemic area, but also produce reactive oxygen species, matrix metalloproteinases, and other substances, leading to increased cell swelling, impaired blood-brain barrier function, and increased vascular permeability. These effects aggravate brain edema and brain damage in patients, thereby affecting the seriousness and outcome of ischemic stroke [16-18].

The levels of lymphocytes reflect the immune situation in the body cells and humoral immunity. After the onset of ischemic stroke, the infarct site is severely stressed due to ischemia and hypoxia, leading to pulsed release of endogenous corticosteroid hormones into the bloodstream. This causes peripheral blood lymphocytes to undergo apoptosis, resulting in significant reduction in the number of peripheral blood lymphocytes. The more extensive the infarct site in patients, the more severe the stress response, the more the corticosteroid hormones enter the bloodstream, and the more significant the reduction in the number of lymphocytes [19,20].

The NLR in peripheral blood integrates two different leukocyte sub-types, i.e., lymphocytes and neutrophils. Therefore, an increase in NLR levels often indicates that the wider the range of stroke in patients, the more severe the disease, and the worse the prognosis. This study found that pre-medication levels of polymorphonuclear leukocytes, neutrophil count, and NLR ratio, were similar in the 2 cohorts. However, post-medication polymorphonuclear leukocyte count, neutrophil count, and NLR ratio were markedly less in the study cohort than the pre-treatment values, and also less than the control cohort counts. Butylphthalide directly acts on vascular endothelial cells, and it decreases brain tissue inflammatory factor levels, reduces inflammation, maintains the integrity of the blood-brain barrier, relieves cerebral vasospasm, improves cerebral blood flow recovery, and quickly restores cerebral blood supply and oxygenation. Moreover, it increases cerebral tissue's partial pressure of oxygen and promotes scavenging of oxygen free radicals, thereby preventing further necrosis of ischemic hypoxic brain tissue, reducing harmful factor increases after brain damage, and effectively protecting brain tissue and brain nerve function [21].

Limitations of this study

The study was carried out in only one study center. Furthermore, the patient population is not statistically sufficient to generalize the outcome of these findings on other patients from other ethnic or geographical goups. Finally, these investigations did not examine the molecular mechanisms of the improved efficacy that was observed as well as the effect of other related factors.

CONCLUSION

The efficacy of combining butylphthalide and edaravone with rt-PA intravenous thrombolysis in

the treatment of ischemic stroke patients was significant. Therefore, the treatment is beneficial for regulating abnormal levels of inflammatory cells, improving coagulation status and reducing the levels of inflammatory factors, thereby alleviating defects in neurological function and enhancing activities of daily living. Further studies using a larger patient population to determine the mechanism of improved efficacy of this combination therapy and the effect of other co-founding factors are required to enhance the validity of these findings.

DECLARATIONS

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None provided.

Ethical approval

The Ethics Committee of the First Affiliated Hospital of Xi'an Medical University, Xi'an, China approved the study (xmu2021006).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Huiyun Ren designed the study, supervised the data collection, and analyzed the data. Xiao Zhe interpreted the data and prepared the manuscript for publication. Shijun Zhang supervised the data collection, analyzed the data and reviewed the draft of the manuscript.

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