Clinical Efficacy of Edaravone and Urinary Kallidinogenase Co-Treatment in Acute Ischemic Stroke

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To evaluate the clinical effectiveness of utilizing edaravone in conjunction with uric acid in treating acute ischemic stroke. Between January 2021 and January 2023, 120 individuals with acute ischemic stroke were admitted to the neurology department of our hospital and were subsequently divided into the observation group and the control group through random assignment. Edaravone monotherapy was utilized in the control group, while the observation group received a combination treatment of edaravone and uric acid. Prior to treatment and post-treatment, the levels of high-sensitivity C-reactive protein and tumor necrosis factor-alpha in the bloodstream were analyzed, while also documenting the overall effective rate and the occurrence of adverse reactions. Post-treatment, a considerable decline was observed in national institutes of health stroke scale and activities of daily living scores for both groups in comparison to their respective pre-treatment scores. Furthermore, the observation group displayed significantly lower national institutes of health stroke scale and activities of daily living scores compared to the control group after treatment, with a $p<0.05$. The observation group exhibited a remarkably higher overall effective rate compared to the control group, with statistical significance ($p<0.05$). Additionally, post-treatment, the levels of inflammatory factors in the observation group were notably lower as opposed to the control group. There was no statistically significant distinction in the incidence of adverse reactions between the two groups ($p>0.05$). The co-administration of edaravone and uric acid in treating acute ischemic stroke may effectively mitigate brain tissue damage by modulating the body's inflammatory response. As a result, it facilitates neurological recovery and enhances the daily living abilities of patients. The significant advantages derived from this treatment approach underscore the importance of promoting its implementation.

Key words: Edaravone, uric acid, combination therapy, acute ischemic stroke, clinical efficacy

In clinical practice, Acute Ischemic Stroke (AIS) is frequently encountered as a cerebrovascular disease, distinguished by its rapid onset and progression[1]. The crucial aspect of managing this condition involves expeditiously reestablishing blood flow, minimizing infarct size, preventing further progression, and preserving neurons from impending demise[2-4]. Currently, there are limited drugs available in China to effectively and safely treat AIS, and recombinant tissue Plasminogen Activator (rt-PA) thrombolysis has shown significant efficacy[5,6], although strict time requirements must be met[7,8]. Additionally, complications such as intracranial hemorrhage and reperfusion injury may occur during the treatment process[9], resulting in a relatively small number of patients truly benefiting from this treatment. From the patient's perspective, the key lies in protecting the nervous system through treatment interventions. Edaravone is widely utilized as a medication in the clinical management of AIS[10,11]. It functions as a free radical scavenger, with a small molecular weight and lipophilic groups that allow it to penetrate the blood-brain barrier and directly act on the lesion site, clearing free radicals and inhibiting lipid peroxidation[12]. These actions help alleviate brain tissue damage and cerebral edema caused by cerebral ischemia[13]. Urinary Kallidinogenase (UK), containing human kininogenase as its active component, is an

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emerging medication employed for the management of AIS. The medication exhibits multiple mechanisms of action. On one hand, it can dilate ischemic small arteries, improve microcirculation in brain tissue, promote glucose utilization, inhibit blood coagulation and platelet aggregation, and stimulate the neovascularization of lesion vessels[14]. On the other hand, it can suppress oxidative stress and inflammatory reactions occurring during cerebral tissue reperfusion[2,15]. Based on the pharmacological characteristics and mechanisms of action of Edaravone and UK, the combined use of these two drugs is expected to provide a comprehensive treatment approach for AIS through multiple pathways, potentially yielding more significant therapeutic effects. However, there is currently a lack of sufficient clinical trial evidence supporting the effectiveness and safety of this combined treatment strategy. This study seeks to evaluate the clinical efficacy of the combined therapy involving edaravone and UK in AIS, employing clinical observations. By analyzing and comparing the recovery of neurological deficits, daily living abilities, serum inflammatory responses, and adverse reactions in both the combined treatment group and control group, we hope to provide scientific evidence for clinical practice. Between January 2021 and January 2023, 120 individuals with AIS were admitted to the neurology department of our hospital and were subsequently divided into the observation group and the control group through random assignment, with 60 cases in each group. In the observation group, there were 38 males and 22 females, aged between 42 y and 79 y old, with an average age of (61.53±6.69) y. The onset time ranged from 6 h to 47 h, with an average of (11.39±2.24) h. The comorbidities included 18 cases of hypertension, 9 cases of diabetes mellitus, and 14 cases of hyperlipidemia. In the control group, there were 36 males and 24 females, aged between 44 y and 78 y old, with an average age of (61.28±6.37) y. The onset time ranged from 7 h to 47 h, with an average of (11.73±4.55) h. The comorbidities included 16 cases of hypertension, 9 cases of diabetes mellitus, and 15 cases of hyperlipidemia. No notable disparities in baseline characteristics, such as comorbidities, age, sex, and onset time, were identified between the two groups, implying comparability. The confirmed diagnosis of AIS through head Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) examination, in accordance with the diagnostic criteria of AIS as documented in the literature[16]; age between 18 y and 80 y; first onset of stroke with a disease duration of less than 48 h; National Institutes of Health Stroke Scale (NIHSS) score between 4 and 20; informed consent obtained were included. The history of traumatic brain injury or brain tumor; seizures or consciousness disorders; severe heart, liver, or kidney diseases; bleeding tendencies; allergy to the drugs used in the study and pregnant or lactating women were excluded. Upon admission, patient's conditions were promptly assessed. For patients eligible for thrombolysis, prompt intravenous thrombolysis was administered, along with anticoagulation, lipid-lowering, microcirculation improvement, and blood pressure management. The control group received treatment with edaravone (National Medical Products Administration Approval Number: H20070051, Manufacturer: Jilin Bodao Pharmaceutical, 10 ml: 15 mg). A total of 30 mg of edaravone was dissolved in 100 ml of 0.9 % sodium chloride solution and administered to the patient *via* intravenous infusion twice daily. The observation group received combined treatment with UK (National Medical Products Administration Approval Number: H20052065, Manufacturer: Tianpu Biochemical Medicine, 0.15 Peptide Nucleic Acid (PNA) units/vial) and edaravone. A total of 0.15 PNA units of UK were added to 100 ml of 0.9 % sodium chloride injection solution, with the infusion rate controlled at 30-40 drops per minute, once daily. The administration method and dosage of edaravone were the same as in the control group. A treatment course lasted for 14 d, and both groups received one treatment course. Prior to and after treatment, the neurological deficits of patients in both groups were evaluated utilizing the NIHSS[17]. To assess daily living abilities, scores from the Activities of Daily Living (ADL) scale were utilized. High-sensitivity C-Reactive Protein (hs-CRP) levels were measured using immunonephelometric assay, and Tumor Necrosis Factor-Alpha (TNF-α) levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA). The overall effective rate of treatment and the incidence of adverse reactions were recorded. A decrease in NIHSS score of >90 % was considered a complete recovery, a decrease

of 46 %-90 % was considered significant improvement, a decrease of 18 %-45 % was considered effective, and decrease of <18 % was considered ineffective. Statistical Package for the Social Sciences (SPSS) 25.0 will be utilized to perform the statistical analysis in this research. Continuous variables will be reported as means and standard deviations (x±s) and analyzed using t-tests. Categorical variables will be presented as frequencies and percentages (n (%)) and analyzed using Chi-square (χ^2) tests. To establish statistical significance, a significance level of $p<0.05$ will be employed. Prior to treatment, no notable disparities were observed in NIHSS scores and ADL scores between the two groups ($p>0.05$). Following treatment, both groups exhibited significant decreases in NIHSS and ADL scores when compared to pre-treatment values, with the observation group demonstrating lower post-treatment scores than the control group ($p<0.05$) as shown in Table 1. The observation group had a remarkably higher overall effective rate of treatment (95.0 %) than the control group (80.0 %) ($p<0.05$) as shown in Table 2. Prior to treatment, there were no noteworthy disparities in hs-CRP and TNF-α levels observed between the two groups. Following treatment, both groups exhibited significant decreases in hs-CRP and TNF-α levels, with the observation group showing a more prominent reduction ($p<0.05$) as shown in Table 3. Both groups encountered adverse reactions, such as dizziness, tinnitus, subcutaneous bruising, and rash. Nonetheless, these reactions did not hinder the progress of the disease treatment. The incidence of adverse reactions did not significantly differ between the two groups ($p>0.05$) as shown in Table 4. An often-occurring and severe ailment, AIS holds great significance in terms of restoring patient's neurological function and enhancing their overall quality of life. The objective of this research was to assess the clinical effectiveness of a combined treatment involving edaravone and UK in patients with AIS. Additionally, the research aimed to investigate the potential therapeutic mechanisms by analyzing clinical and biochemical alterations. Firstly, we observed a notable advantage in the improvement of neurological function in individuals treated with edaravone and UK. Using NIHSS and ADL assessments, we found that the NIHSS scores significantly decreased in both groups following treatment, indicating improved neurological function. Comparatively, the observation group exhibited notably lower NIHSS and ADL scores in contrast to the control group, indicating a favorable impact of the combined treatment on ameliorating neurological deficits and enhancing daily living abilities. These findings align with observations from other relevant studies, further substantiating the effectiveness of the combined therapy involving edaravone and UK[18]. Additionally, by analyzing indicators of systemic inflammatory response, we revealed the possible therapeutic mechanisms of the combined treatment. After AIS, levels of inflammatory factors may rise, potentially damaging neurons and exacerbating neurological impairments[3]. In our study, we found that after treatment, the levels of hs-CRP and TNF-α in the observation group were significantly lower than those in the control group. This suggests that combined treatment with edaravone and UK may alleviate brain tissue damage by suppressing post-injury inflammatory responses, thus promoting neurological recovery. This result aligns with findings from prior studies and reinforces the importance of the inflammatory mechanism in the treatment of stroke[19]. Furthermore, our findings showed that the observation group had a remarkably higher overall effective rate than the control group. The improvement in the overall effective rate relies on a comprehensive evaluation of neurological function recovery and disease prognosis. Therefore, combined treatment with edaravone and UK is also feasible in improving the overall treatment efficacy of patients. Nonetheless, there exist certain limitations to this study. Firstly, the relatively small sample size potentially undermines the reliability and generalizability of the findings. Thus, it is imperative to conduct large-scale, multicenter, randomized controlled trials to comprehensively evaluate the effectiveness and safety of the combined treatment involving edaravone and UK. Secondly, the treatment duration was relatively brief, making it impossible to assess long-term efficacy and prognostic outcomes. Future investigations should extend the follow-up period to acquire a more comprehensive evaluation of treatment efficacy. To conclude, this study's results highlight significant advantages for the observation group, including improved recovery of neurological function, enhanced daily living

abilities, regulation of the inflammatory response, and overall treatment effectiveness in the combined approach utilizing edaravone and UK. These results strongly advocate for the utilization of the combined treatment approach in individuals with AIS. Further research with larger sample sizes and extended follow-up periods is warranted to further substantiate and investigate the efficacy, mechanisms, and safety of the combined treatment, thus yielding more dependable evidence for clinical practice.

TABLE 1: COMPARISON OF NIHSS SCORE

Group (n=60)	NIHSS		ADL	
	Before	After	Before	After
Observation	19.50±1.59	8.17±5.07*	3.88±1.28	1.62±1.08*
Control	19.47±1.60	10.50±5.62*	3.70±1.38	2.53±1.12*
t	0.063	2.112	-0.561	4.974
p	0.95	0.037	0.576	0.000

Note: *p<0.05, indicates significant difference after treatment compared with before treatment

TABLE 2: COMPARISON OF CURATIVE EFFECT

Group (n=60)	Cure	Significant	Effective	Invalid	Overall effective rate
Observation	17 (28.3)	22 (36.7)	18 (30.0)	3 (5.0)	57 (95.0)
Control	13 (21.7)	18 (30.0)	17 (28.3)	12 (20.0)	48 (80.0)
χ^2			-		6.171
p			-		0.013

TABLE 3: COMPARISON OF OXIDATIVE STRESS MARKERS

Group (n=60)	hs-CRP (mg/l)		TNF-α (ng/ml)	
	Before	After	Before	After
Observation	11.60±4.09	3.18±1.29*	53.60±17.84	17.48±6.12*
Control	11.50±3.88	7.48±1.58*	53.02±18.76	27.16±7.84*
t	-0.132	16.276	-0.172	7.654
p	0.895	0.000	0.864	0.000

Note: *p<0.05, indicates significant difference after treatment compared with before treatment

TABLE 4: OCCURRENCE OF ADVERSE REACTIONS n (%)

Group (n=60)	Dizziness and tinnitus	Subcutaneous ecchymosis	Rash	Overall incidence
Observation	2 (3.3)	2 (3.3)	3 (5.0)	7 (11.7)
Control	3 (5.0)	2 (3.3)	1 (1.7)	6 (10.0)
χ^2				0.086
p				0.769

Conflict of interests:

The authors declared no conflict of interests.

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