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Original Article

Therapeutic effects of alteplase intravenous thrombolysis on different types of acute cerebral infarction: a controlled randomized analysis

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Abstract: Objective: To test the effects of alteplase (PA) intravenous thrombolysis on different types of acute cerebral infarction (ACI). Methods: One hundred and ten patients with the ACI admitted from April 2018 to April 2019 were selected and randomly assigned to a research group and a reference group equally. The two groups received conventional treatment with a subcutaneous injection of low molecular weight heparin calcium of 5000 IU, and the research group received additional PA intravenous thrombolysis treatment. The therapeutic effects of the two groups were compared. Results: There were no significant differences in terms of general information and National Institutes of Health Stroke Scale (NIHSS) score at T0 ($P>0.05$) between the two groups; the research group garnered better results in the NIHSS scores at T1, T2, T3, and T4 than the reference group ($P<0.001$); a decrease was found in the Modified Rankin Scale (MRS) after treatment ($P<0.001$), with lower scores in the research group ($P<0.001$); the research group obtained a higher total effective rate than the reference group ($P<0.05$). Remarkably higher Barthel scores of the two groups after treatment were found ($P<0.001$), with higher scores collected from the research group ($P<0.001$); patients in the research group enjoyed a lower incidence of bleeding events than the reference group ($P<0.05$). The levels of Interleukin-1β (IL-1β), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and malondialdehyde (MDA) were apparently optimized after treatment, with superior results observed in the research group ($P<0.05$). Conclusion: PA intravenous thrombolysis effectively improves the neurological function of patients with different types of ACI and their quality of life, and reduces bleeding events, which is worthy of promotion.

Keywords: PA intravenous thrombolysis, different types of ACI, therapeutic effects

Introduction

Acute cerebral infarction (ACI) is one of life-threatening diseases with high morbidity, disability, mortality and recurrence rates. With the aging of the population, the rapid development of the economic level and the change of lifestyle, ACI has become a major public health problem [1, 2]. According to the epidemiological survey [3], middle-aged and elderly populations are more vulnerable to the disease, among which male patients are more susceptible than females. Moreover, there has been a trend of gradual rise in the number of patients year by year. It has been clinically confirmed that this disease mostly occurs in patients with coronary atherosclerotic stenosis as a result of the rupture of atherosclerotic plaque with different inducements, which leads to a large amount of platelets in the blood to coagulate on the plaque surface, forming thrombus to block the vascular cavity and inducing acute cerebral infarction (ACI) [4-6]. Thrombolytic therapy yields promising outcomes in dissolving the newly-formed thrombus, reducing the cerebral infarction area to the maximum, improving the ischemic penumbra, maintaining clear cerebral vessels, restoring the normal blood supply to the brain, and optimizing the neurological function. Alteplase (PA) is a frequently used thrombolytic drug with a main component of glycoprotein that can quickly combine with lysine residues after entering human blood vessels, reduce platelet aggregation, and exert signifi-

cant therapeutic effects in improving tissue ischemia and blood flow [7-9]. Based on this, we investigated the therapeutic effects of PA intravenous thrombolysis on different types of ACI.

Subjects and methods

General information

A total of 110 patients with different types of ACI admitted from April 2018 to April 2019 were selected as the objects and assigned into a research group and a reference group, with 55 cases in each group. The study was approved by the Ethics Committee of the Weifang People's Hospital (ClinicalTrials.gov Identifier: NCT03539441. Ethics Certificate Number: 2017-3-26), and the patients signed an informed consent after being fully informed of the purpose and process of the study.

Inclusion criteria

(1) Patients were in line with diagnostic criteria of different types of ACI [10]; (2) Patients with clear consciousness; (3) Visible functional impairment lasted for more than one hour.

Exclusion criteria

(1) Patients who were allergic or intolerant to drugs; (2) Patients who had craniocerebral injury within two months before the study; (3) Patients who had malignant tumor in the meantime; (4) Patients who had mental and other cognitive disorders or refused to cooperate in the experiment.

Methods

The reference group received routine clinical treatment (low molecular weight heparin calcium 5000 IU, subcutaneous injection, 2 times a day, 1 week as a course of treatment). After admission, the patients received sedative and analgesic therapy. The venous channels were established, the blood volume was adjusted, and the balance of intake and output was monitored. The patients were required to stay in bed for 1-3 days during the acute phase, with dynamic monitoring of physiological indexes such as the heart rate, respiration and blood pressure; the patients were instructed to follow a low salt and low fat diet, conduct a daylong stream of mini meals, and keep a normal bowel movement.

On this basis, the research group was additionally treated with PA (SFDA Approval No. S20110052, Manufacturer: Shanghai Kangqiao Pharmaceutical Co., Ltd., Specification: 50 mg/tube/box) intravenous thrombolytic therapy. 0.9 mg/kg PA and 100 ml saline were blended for the maximum drug dosage of 90 mg, among which 10 mg was administered intravenously, and the rest was given by continuous intravenous drip with a moderate dripping speed within 60-70 minutes. The physiological indicators of patients after medication were monitored. The administration continued for 14 days, and the patients of the two groups were followed up for three months.

Observation indexes

Based on the NIHSS [10], neurological deficits at different time points in the two groups were evaluated. The scale has 15 points as its total score. The higher the score, the more serious the neurological deficits. Five time points T0, T1, T2, T3 and T4 were set, corresponding to patients' conditions before treatment, 1 day, 10 days, 30 days and 90 days after treatment.

The neurological recovery in patients of the two groups before and after treatment was evaluated referring to the MRS [11]. The full score of the scale is 5 points, and the lower the MRS score, the better the neurological recovery of the patients.

Curative effect: recovery: more than 90% decrease in the neurological deficit score of patients after treatment; significantly effective: 46%-90% decrease in the neurological deficit score after treatment; effective: 18%-45% decrease in the neurological deficit score after treatment; ineffective: less than 17% in the neurological deficit score or even worsened after treatment. The total effective rate = recovery rate + significant effective + effective rate.

According to Barthel Index Scale [12], the activities of daily living (ADL) of the two groups were evaluated before and after treatment. The full score of the scale is 100 points. The higher the score, the better the patients' ADL.

The clinical bleeding events of the two groups were recorded and compared.

The peripheral blood of the patients was taken before and after the treatment, and the lev-

Table 1. Comparison of clinical data between the two groups [n (%)]

Category	Reference group (n=55)	Research group (n=55)	χ^2/t	P
Gender			0.037	0.848
Male	29 (52.73%)	30 (54.55%)		
Female	26 (47.27%)	25 (45.45%)		
Average age	63.64±3.52	64.61±3.49	1.451	0.150
BMI (kg/m^2)	21.34±1.02	21.36±1.04	0.102	0.919
Systolic blood pressure (mmHg)	141.35±8.73	141.38±8.71	0.018	0.986
Diastolic blood pressure (mmHg)	83.54±7.63	83.52±7.61	0.014	0.989
Blood glucose level (mmol/L)	7.38±1.84	7.36±1.87	0.057	0.955
Disease type (Cases)				
Type 1	7 (12.73%)	8 (14.55%)	0.077	0.781
Type 2	16 (29.09%)	15 (27.27%)	0.045	0.832
Type 3	13 (23.64%)	14 (25.45%)	0.049	0.825
Type 4	12 (21.82%)	10 (18.18%)	0.227	0.634
Type 5	7 (12.73%)	8 (14.55%)	0.077	0.781
Place of residence (Cases)			0.147	0.702
City and town	24 (43.64%)	26 (47.27%)		
Countryside	31 (56.36%)	29 (52.73%)		

els of IL-1β (Product No. KT86579, Wuhan MSKBIO Technology Co., Ltd.), hs-CRP (Product No. KT22657, Wuhan MSKBIO Technology Co., Ltd.), TNF-α (Product No. KT22523, Wuhan MSKBIO Technology Co., Ltd.), MDA (Product No. KT99703, Wuhan MSKBIO Technology Co., Ltd.), SOD (Product No. KT30016, Wuhan MSKBIO Technology Co., Ltd.) and GSH-px (Product No. KT98572, Wuhan MSKBIO Technology Co., Ltd.) were detected by ELISA kits.

Statistical methods

All the experimental data were statistically analyzed by the software SPSS21.0 and graphed by GraphPad Prism 6 (GraphPad Software, San Diego, USA). x^2 test was adopted for comparison of count data [n (%)], while *t*-test was used for the comparison of measurement data ($\bar{x} \pm sd$). The difference was statistically significant with P<0.05.

Results

Comparison of clinical data between the two groups

The two groups presented no statistical difference regarding the general information of the patients (P>0.05), as shown in **Table 1**.

Comparison of NIHSS scores at different time points between the two groups

There was no obvious difference in NIHSS scores at T0 between the two groups (P>0.05), and the NIHSS scores at T1, T2, T3 and T4 of the research group were distinctly lower than those of the reference group (P<0.05), as shown in **Figure 1**.

Comparison of mRS scores before and after treatment between the two groups

After treatment, the MRS scores of the two groups all declined significantly (all P<0.05), but a greater decline of the research group was obtained (P<0.05), as shown in **Figure 2**.

Comparison of clinical efficacy between the two groups

A notably higher total effective rate was observed in the research group, as compared to the reference group (P<0.05), as shown in **Table 2**.

Comparison of Barthel scores between the two groups before and after treatment

After treatment, both groups exhibited a significant increase in Barthel scores as compared with those before treatment (P<0.05), and remarkably higher Barthel scores were identified in the research group than in reference group (P<0.05), as shown in **Table 3**.

Comparison of bleeding events in hospital between the two groups

Table 4 shows that the research group yielded a more favorable outcome in the total incidence

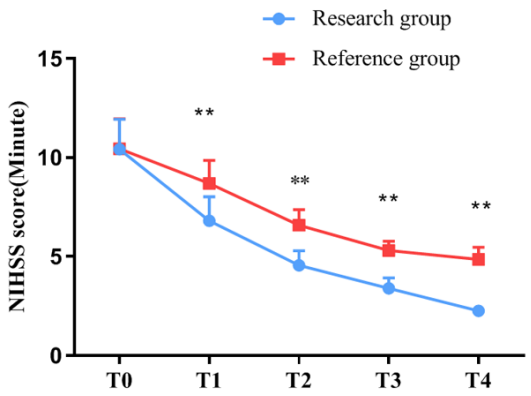

Figure 1. Comparison of NIHSS scores at different time points between the two groups ($\bar{x}$ ± sd). Note: The abscissa represents T0, T1, T2, T3, T4, and the ordinate represents NIHSS scores. In the research group, NIHSS scores at T0, T1, T2, T3 and T4 were 9.35±2.14, 5.94±1.72, 4.03±1.05, 3.02±0.74 and 2.13±0.24, respectively. NIHSS scores of the reference group at T0, T1, T2, T3 and T4 were 9.38±2.13, 7.88±1.64, 6.02±1.12, 4.98±0.65 and 4.43±0.86, respectively. The NIHSS score at T1 was significantly different between the two groups (t=6.054, **P<0.01). The NIHSS score at T2 was significantly different between the two groups (t=9.613, **P<0.01). The NIHSS score at T3 was significantly different between the two groups (t=14.758, **P<0.01). The NIHSS score at T4 was significantly different between the two groups (t=19.104, **P<0.01).

of bleeding events than the reference group (P<0.05).

Comparison of IL-1β, hs-CRP, TNF-α and SOD levels between the two groups

Before treatment, the levels of IL-1β, hs-CRP, TNF-α and SOD between the two groups of patients were not statistically different (all P>0.05); after treatment, the levels of IL-1β, hs-CR, TNF-α and SOD in the two groups were improved compared with those before treatment, with lower levels of IL-1β, hs-CRP, TNF-α and SOD in the research group than those in the reference group (P<0.05). See **Table 5**.

Comparison of GSH-px and MDA levels between the two groups

The two groups showed no apparent difference in the levels of GSH-px and MDA before intervention (P>0.05); after treatment, the levels of GSH-px and MDA in the two groups were optimized compared to those before treatment, and higher GSH-px and lower MDA levels in the

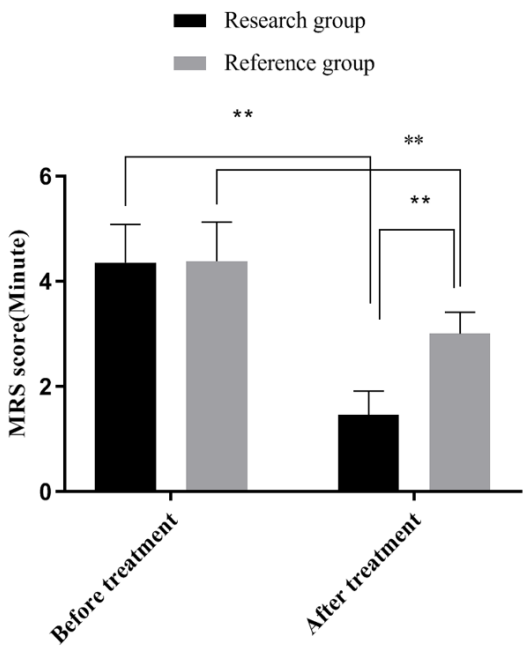

Figure 2. Comparison of *MRS* scores between the two groups before and after treatment ($\bar{x}$ ± sd). Note: The abscissa represents conditions before and after treatment, and the ordinate represents MRS scores. The MRS scores of the research group before and after treatment were 3.84±1.03 and 1.15±0.63, respectively. The *MRS* scores of the reference group before and after treatment were 3.86±1.05 and 2.71±0.58, respectively. The *MRS* scores before and after treatment were significantly different in the research group (t=16.523, **P<0.01). The *MRS* scores before and after treatment were significantly different in the reference group (t=7.110, **P<0.01). The *MRS* scores after treatment were significantly different between the two groups (t=13.510, **P<0.01).

research group than those of the reference group were recorded (P<0.05). See **Table 6**.

Discussions

Generally, ACI patients are divided into two main subtypes according to TOAST classification [13], namely large atherosclerotic cerebral infarction and small artery occlusion/lacunar infarction, which is also known as ischemic stroke, a neurological function deficit syndrome with the blood shortage or interruption in brain tissue caused by different reasons [13-15].

Clinical studies showed that the brain tissues are extremely sensitive to hypoxia and ischemia. Metabolic changes start in brain cells 30 seconds after the interruption of blood supply, the brain stops functioning after 60 seconds,

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Category	n	Recovery	Significantly effective	Effective	Ineffective	Total effective rate
Research group	55	18 (32.73%)	17 (30.91%)	18 (32.73%)	2 (3.64%)	96.36% (53/55)
Reference group	55	10 (18.18%)	16 (29.09%)	19 (34.55%)	10 (18.18%)	81.82% (45/55)
X^2						5.986
P						0.014

Table 3. Comparison of Barthel scores between the two groups before and after treatment ($\bar{x} \pm sd$, points)

Category	Before treatment	After treatment	T_2	P_2
Research group (n=55)	44.18±2.76	76.53±3.62	52.704	0.001
Reference group (n=55)	44.21±2.74	58.74±3.27	25.258	0.002
T_1	0.057	27.045		
P_1	0.955	0.001		

Note: T_1 and P_1 represent the intergroup comparison of Barthel scores before and after treatment, and T_2 and P_2 represent the intra-group comparison of Barthel scores before and after treatment.

Table 4. Comparison of bleeding events in the hospital between the two groups [n (%)]

Category	n	Gingival hemorrhage	Intracranial hemorrhage	Hematuria	Gastrointestinal hemorrhage	Total incidence rate
Research group	55	2 (3.64%)	0 (0.00%)	1 (1.81%)	0 (0.00%)	5.45% (3/55)
Reference group	55	4 (7.27%)	1 (1.81%)	3 (5.45%)	3 (5.45%)	20.00% (11/55)
X^2						5.238
P						0.022

Table 5. Comparison of IL-1β, hs-CRP, TNF-α and SOD levels between the two groups of patients ($\bar{x} \pm sd$)

Index	Time	Research group (n=55)	Reference group (n=55)	t	P
IL-1β (pg/ml)	Before treatment	245.39±34.63	246.88±31.06	1.369	0.896
	After treatment	140.36±11.36	178.96±13.88	14.523	0.001
	t	12.639	13.654		
	P	0.001	0.002		
hs-CRP (mg/ml)	Before treatment	13.54±3.64	13.48±3.67	2.367	0.965
	After treatment	8.49±2.39	10.56±2.89	4.536	0.001
	t	4.639	8.654		
	P	0.002	0.001		
TNF-α (pg/ml)	Before treatment	379.39±25.13	380.28±24.06	1.369	0.887
	After treatment	126.56±21.46	182.96±23.88	10.123	0.001
	t	42.639	43.698		
	P	0.001	0.002		
SOD (U/ml)	Before treatment	4.17±0.75	4.05±0.69	1.654	0.945
	After treatment	8.49±2.39	10.56±2.89	3.697	0.001
	t	5.369	4.697		
	P	0.002	0.001		

and brain cells begin to die after 4 minutes. Therefore, it is of great significance for patients with ACI to receive a timely and effective treatment to further drive down the morbidity [16,

Table 6. Comparison of GSH-px and MDA levels between the two groups

Groups	GSH-px (mmol/L)				MDA (mmol/L)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Research group (n=55)	27.01±8.63	47.39±17.91	12.569	0.001	9.32±1.75	5.57±1.01	5.369	0.005
Reference group (n=55)	26.99±8.13	35.78±12.36	13.554	0.002	9.29±1.66	7.75±1.26	7.369	0.002
t	8.369	1.367			7.369	1.574		
P	0.268	0.002			0.365	0.001		

17]. A number of studies have shown a more prominent clinical application value of PA in the treatment of ACI within 3 to 4.5 hours from onset to administration, which is considered a positive therapeutic window. It substantially promotes the recanalization of blood flow in the cerebral infarction area, accelerates the restoration of the blood supply of the ischemic penumbra, secures a high tolerance of the patients and enjoys less adverse reactions. The treatment of ACI with PA within 3 to 4.5 hours from onset to administration can achieve significant clinical effects in reducing the neurological deficits with high safety [18, 19].

The key of ACI first aid requires a quick elimination of the cerebrovascular obstruction in patients and a restoration of the blood supply function. Intravenous thrombolytic therapy is an effective measure to dredge the cerebrovascular and restore blood perfusion, which has been recommended by many national medical institutions. Sun et al. [19] confirmed that a cascade of physiological changes will occur to human body, including the release of a large number of oxygen free radicals after brain damage, which causes damages to cell membrane and organelles and results in the large-scale death of nerve cells. If timely and effective treatment can be implemented, the recovery of blood circulation in the ischemic penumbra can be promoted and necrotic tissue can be optimized. In this study, PA was used in intravenous thrombolytic therapy, and the after-treatment scores of NIHSS at different time points dropped more drastically than those in the reference group (P<0.001), suggesting that PA intravenous thrombolytic therapy effectively improved patients' neurological function and prognosis. The NIHSS score is a key index for the evaluation of neurological function recovery in patients with acute stroke, which is simple and reliable in application [20] and can be evaluated by non-neurologists in clinical identification. In addition, this study also found that the Barthel scores of patients after treatment was elevated more significantly than that of the reference group (P<0.001), which was consistent to the conclusion of a previous study [21]. In addition, the occurrence of few cases of bleeding after the treatment of PA intravenous thrombolysis emphasized the significance of clinical monitoring. The levels of IL-1β, hs-CRP, TNF-α, SOD, GSH-px, and MDA in the two groups were remarkably ameliorated after treatment, with a more promising result obtained in the research group, indicating that intravenous thrombolysis with PA can reduce the level of inflammatory factors and improve the stress response of patients. The innovation of this study lies in the combination of the drugs to relieve cerebral infarction, and the amelioration effect of PA on patients' neurological deficits. Thus, a better therapeutic effect can be achieved.

In conclusion, PA intravenous thrombolytic therapy effectively improve patients' neurological function with different types of ACI and their ADL with high safety, which is worthy of promotion and clinical application.

Disclosure of conflict of interest

None.

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