Am J Transl Res 2021;13(12):14005-14014
www.ajtr.org /ISSN:1943-8141/AJTR0138139

Original Article

Effects of cerebral artery thrombectomy on efficacy, safety, cognitive function and peripheral blood Aβ, IL-6 and TNF-α levels in patients with acute cerebral infarction

Chun Chen[1,2*], Yiyi Zhu[2*], Yan Chen[1*], Zengjun Wang[2], Liandong Zhao[2]

[1]Department of Neurological Medicine, Siyang Hospital of Traditional Chinese Medicine, Siyang 223700, Jiangsu Province, China; [2]Department of Neurology, Xuzhou Medical University Affiliated Hospital of Huai'an, Huai'an 223002, Jiangsu Province, China. [*]Equal contributors.

Received August 9, 2021; Accepted November 3, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objective: Acute cerebral infarction (ACI) can lead to death or disability, posing a serious threat to human health. This study aimed to investigate the effects of cerebral artery thrombectomy on the efficacy, safety, cognitive function and peripheral blood amyloid-β (Aβ), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels in patients with ACI. Methods: The clinical data of 169 patients with ACI admitted to our hospital from April 2019 to September 2020 were analyzed retrospectively. Among them, 100 patients were treated with cerebral artery thrombectomy and assigned to the research group, and the other 69 patients were intervened by conventional treatment and assigned to the control group. The clinical effects in the two groups were observed and compared. The cognitive function was evaluated by the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Scale (MoCA), the neurological dysfunction was assessed by the National Institutes of Health Stroke Scale (NIHSS), and the prognosis was determined by the Modified Rankin Scale (mRS). Peripheral blood Aβ1-40, Aβ1-42, IL-6 and TNF-α levels were determined using the enzyme-linked immunosorbent assay (ELISA). The incidence of adverse reactions and complications was statistically analyzed. Results: The overall response rate (ORR) was notably higher in the research group compared with the control group. Aβ1-40, Aβ1-42, IL-6 and TNF-α levels showed no significant difference between the two groups before treatment (P>0.05). After treatment, serum Aβ1-40 level was lower and Aβ1-42 was higher in the research group compared with the control group at each time point. Serum IL-6 level was markedly higher within 24 h while it was dramatically lower 24 h after treatment in the research group as compared with the control group. At 24 h, 7 d and 14 d after treatment, serum TNF-α level in the research group was lower than that in the control group (P<0.05). The MMSE and MoCA scores showed no significant differences between the two groups before treatment; however, the two scores in the research group were statistically higher than those in the control group after treatment. In addition, lower NIHSS and mRS scores were determined in the research group compared with the control group after treatment. Moreover, except for the statistically significant difference in the number of cases with cognitive dysfunction (P<0.05), there was no significant difference in the incidence of other adverse reactions between the research group and the control group (P>0.05). Conclusions: Cerebral artery thrombectomy is effective in the treatment of ACI, which can improve the cognitive function of patients and alleviate the high Aβ accumulation and inflammation in the central nervous system, with a high safety profile.

Keywords: Acute cerebral infarction, cerebral artery thrombectomy, efficacy, security, cognitive function

Introduction

Acute cerebral infarction (ACI) is a serious cerebrovascular infarction disease, which refers to a clinical event in which acute circulatory disturbances in the cerebral arteries lead to tissue ischemia and hypoxia and cause cerebral dysfunction rapidly [1]. Characterized by rapid onset, high morbidity and mortality, ACI shows an increasing incidence year by year, which has become a common disease that seriously threatens human health and life expectancy [2, 3]. After the attack of ACI, there is a penumbra zone surrounding the ischemic necrosis center.

If the blood supply to the infarct area is restored in time, the brain cells in the penumbra zone will survive. Therefore, the degree of injury recovery of the penumbra zone plays a decisive role in the prognosis of patients [4]. On the other hand, the lack of effective and timely treatment measures will lead to impairment of cognitive function. Mild cognitive function is prone to causing vascular dementia, which will not only impair the physical mobility of patients, but also lead to reduced quality of life and poor clinical outcomes [5, 6].

At present, the pathogenesis of acute progressive cerebral infarction remains elusive, but it is clinically believed to be associated with many factors such as brain edema, hypoperfusion, and reperfusion injury [7, 8]. Statistics show that [9], patients with ACI will develop sequelae of varying degrees, with more than a half suffering from severe sequelae, which greatly reduces the quality of life of patients and seriously restricts their family life experience. Therefore, it is of utmost importance to take scientific and effective measures once ACI is diagnosed. Cerebral artery thrombectomy is a minimally invasive procedure [10]. With the help of digital subtraction angiography (DSA) technology, the neck and intracranial vessels are developed by puncture of the femoral artery and injection of contrast agent, and the guide wire and stent are delivered to the diseased vessels. Then, the embolus is anchored and released by the above tools, and the embolus is removed from the body until it is removed as far as possible to ensure the integrity of the embolus [11]. Restoring the patency of occluded blood vessels through cerebral artery thrombectomy can restore effective blood supply in time, promote the rapid regression of inflammatory response after reaching the peak, and protect neurons in a relatively stable environment, so that the brain functional areas including cognitive function are expected to be spared; hence, cerebral artery thrombectomy has gradually become a more ideal treatment for ACI patients [12, 13]. Studies [14-16] have found that when hemodynamic disorders occurred in the brain, there were abnormally increased levels and accumulation of amyloid-β (Aβ), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in the brain due to blocked blood flow as well as oxidative stress and inflammatory response. Hemodynamic disorders will also damage the function of blood-brain barrier (BBB) and change its permeability, which makes it easier for Aβ, IL-6 and TNF-α to enter the central nervous system. Aβ is a metabolite of Aβ precursor protein, and its generation and clearance are generally in a dynamic equilibrium [17]. But when the balance is destroyed by some factors, it will accumulate in the central nervous system, especially in neuron-rich areas such as the hippocampus, thus damaging nerve cells and affecting cognitive function.

In this study, cerebral artery thrombectomy was performed to restore the cerebral blood flow (CBF) in patients with ACI, and its effects on the efficacy, safety, cognitive function and peripheral blood Aβ, IL-6 and TNF-α were observed and compared.

Materials and methods

Study population

The clinical data of 169 ACI patients admitted to our hospital from April 2019 to September 2020 were collected and analyzed retrospectively. The patients were allocated into a control group (n=69) and a research group (n=100) according to different treatment methods. Inclusion criteria: Patients with age ≥18 years; Patients with acute anterior circulation large vessel occlusive stroke within 6 hours of onset; Patients with confirmed aortic occlusion by DSA or magnetic resonance angiography (MRA) imaging examination, with clinical symptoms or signs corresponding to the suspected occluded vascular dominance area; Patients with the Modified Rankin Scale (mRS) score of 0 or 1 before onset, and the National Institutes of Health Stroke Scale (NIHSS) ≥6 at onset; Patients with the Alberta Stroke Program Early Computed Tomographic Score (ASPECT) ≥6 in plain head CT scan; Patients or their immediate families had provided informed consent after informing them of the relevant information about this study. Exclusion criteria: Patients with Encephalorrhagia or subarachnoid hemorrhage indicated by head CT; Patients with a history of craniocerebral trauma in recent 3 months or a history of craniocerebral operation in recent 2 weeks; Patients with severe heart, liver and kidney insufficiency; Patients in pregnancy; Patients with severe

Table 1. General baseline data

	Control group (n=69)	Research group (n=100)	χ^2/t	P
Age (years)	63.95±4.26	64.54±5.03	0.7967	0.4267
Gender				
Male	41	58		
Female	28	42		
BMI (kg/m^2)	23.97±2.66	24.34±3.48	0.7454	0.4709
Duration from onset to treatment (h)	4.05±1.08	4.14±1.12	0.5209	0.6031
Infarction area (cm^3)	30.84±4.97	31.28±5.21	0.5498	0.5832
Infarction site and number of emboli				
Middle cerebral artery	40	52	0.5869	0.4436
Single	32	37	0.9436	0.3314
Multiple	8	15		
Internal carotid	29	48	0.5869	0.4436
Single	22	35	0.0816	0.7752
Multiple	7	13		
History of hypertension	21	39	1.3081	0.2527
History of diabetes	16	25	0.0729	0.7871
Hyperlipoidemia	18	24	0.0952	0.7576
History of smoking	19	29	0.0430	0.8357
History of drinking	16	31	1.2411	0.2653
Atrial fibrillation	17	22	0.1600	0.6891

Note: BMI, body mass index.

hypertension beyond the control of drugs (systolic pressure ≥180 mmHg or diastolic pressure ≥100 mmHg); Blood glucose <2.7 mmol/L or >22.2 mmol/L; Patients with abnormal blood coagulation international normalized ratio (INR) >1.7 or platelet count <100 × 10^9/L; Patients with life expectancy <90 days; Patients with a history of cognitive impairment prior to treatment; Patients who refused to collect blood or failed to follow up; Patients with massive cerebral infarction or symptomatic hemorrhage after treatment. The general baseline data were similar and comparable between the two groups (P>0.05, **Table 1**). The study was approved by the Institutional Board Review at Xuzhou Medical University Affiliated Hospital of Huai'an.

Treatment methods

Patients in the control group were treated with routine neurological treatment such as antiplatelet, lipid regulation, brain protection, nerve nutrition and blood pressure control.

Patients in the research group received cerebral artery thrombectomy. The patient was given 2% lidocaine for local anesthesia after routine disinfection of bilateral groin areas and towel laying. The right femoral artery was punctured by the modified Seldinger method, and a 6F arterial catheter sheath was inserted. Then, continuous infusion of normal saline with high pressure was performed. Thereafter, a 5F catheter was delivered via the artery sheath. Four whole brain angiograms were performed to confirm the occlusion site. After that, the 5F angiography catheter was withdrawn and a 6F guiding catheter was inserted. The Reber27 microcatheter was sent to the distal end of obstructed cerebral artery via the guide catheter with the aid of 0.014 micro-guide wire. After the cavity was confirmed by microcatheterization, the Solitaire stent was sent to the occlusion part to open the stent, so that the stent completely covered the occlusion segment. After 5-10 min, the flushing water was turned off, the catheter balloon was dilated to seal the proximal blood flow, and the stent and the thrombus were pulled into the catheter and removed from the body. After stent removal, angiography was performed again. Thrombectomy was completed if the modified thrombolysis in cerebral infarction (mTICI) of the occluded vessel was ≥2b and can be main-

tained when angiography was performed 15 minutes later. If the above criteria were not reached, thrombectomy was performed again to restore CBF. If the stenosis at occlusion site remained severe, the stent was implanted after balloon dilatation. After thrombectomy, the research group received the same routine neurological treatment as the control group.

Endpoints

(1) After treatment, all patients were reexamined by cerebral angiography and evaluated by the Thrombolysis in Cerebral Infarction (TICI) classification for therapeutic efficacy. TICI III: complete recanalization of blood vessels after treatment; TICI II: partial recanalization of blood vessels; TICI 0-I: failure of recanalization. The overall response rate (ORR) = (grade II + grade III) cases/total cases × 100%.

(2) Serum Aβ1-40, Aβ1-43, IL-6, TNF-α levels: Cubital venous blood was extracted before treatment as well as 2 h, 24 h, 7 d and 14 d after treatment and centrifuged at 1000 r/min for 10 minutes. The resultant supernatant was measured using the Enzyme Linked Immunosorbent Assay (ELISA) for serum Aβ1-40, Aβ1-42, IL-6 and TNF-α levels with kits all purchased from Nanjing Jiancheng Bioengineering Institute, strictly following the kit instructions. The optical density (OD) of each group was measured at 450 nm with a microplate reader (DG5033A, Nanjing Huadong Electronic Information & Technology Co., Ltd).

(3) Neurological dysfunction: Before treatment as well as 2 h, 24 h, 7 d and 14 d after treatment, the severity of stroke of patients was evaluated using the National Institutes of Health Stroke Scale (NIHSS) scale, which was scored from 11 dimensions such as level of consciousness, level of consciousness questions, level of consciousness commands, best gaze, visual and facial palsy. The higher the NIHSS score, the more severe the brain function damage.

(4) The mental state of patients before and after treatment was scored by the Mini-Mental State Examination (MMSE) scale from five dimensions of orientation, registration, attention and calculation, recall and language ability. The total score of the scale was 30 points, and higher scores indicated better recovery of the mental state. The evaluation of cognitive status of patients before and after treatment employed the Montreal Cognitive Assessment Scale (MoCA). The total score of the scale was 30 points, and higher scores indicated better cognitive status of patients. The evaluation time was 30 days before and 90 days after treatment.

(5) Patient prognosis was assessed using the Modified Rankin Scale (mRS): 0 - no symptoms; 1 point - no obvious disability despite some symptoms, able to perform all usual duties and activities; 2 points - slight disability, unable to conduct all previous activities, but able to look after own affairs without assistance; 3 points - moderate disability, requires some help, but able to walk unassisted; 4 points - moderately severe disability, unable to walk unassisted and unable to attend to own bodily needs without assistance; 5 points - severe disability, bedridden, incontinent, and requiring constant nursing care and attention; 6 points - dead. The patients' functional recovery was scored by the mRS before treatment and on the 30th and 90th day after treatment.

(6) The common complications or adverse reactions were observed after treatment, including encephalorrhagia, vascular re-occlusion, ischemia-reperfusion injury, cerebral vasospasm, severe headache and cognitive dysfunction, and the incidence of various complications and adverse reactions were calculated.

The primary outcome measure is clinical efficacy, and the secondary indicators are serum Aβ1-40, Aβ1-43, IL-6 and TNF-α levels as well as other functional scale scores (MMSE, MoCA, mRS) and complication rate.

Statistical processing

SPSS 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were recorded as mean ± standard deviation and analyzed using the t test. Categorical variables were described as percentages (%) and analyzed by the Chi-square test. Differences between the mean values were determined by analysis of variance with or without repeated measurements, followed by Bonferroni post hoc test. With $\alpha=0.05$ as the test standard, the difference was statistically significant when $P<0.05$.

Table 2. Comparison of clinical efficacy between the two groups

	Grade 0	Grade I	Grade II	Grade III	Overall response rate
Control group (n=69)	4 (5.8)	10 (14.5)	19 (27.5)	36 (52.2)	55 (79.9)
Research group (n=100)	0 (0)	9 (9.0)	24 (24.0)	67 (67.0)	91 (91.0)
χ^2					4.4261
P					0.0354

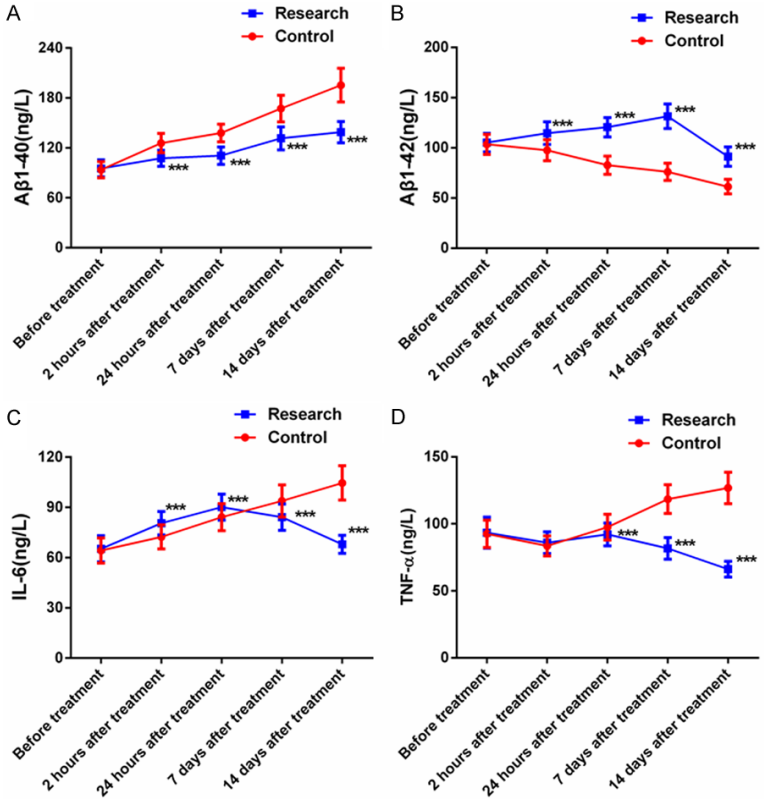

Figure 1. Levels of serum Aβ1-40, Aβ1-42, IL-6 and TNF-α in the two groups. A: Aβ1-40 level; B: Aβ1-42 level; C: IL-6 level; D: TNF-α level; ***P<0.001 vs. the control group at the same time point. Note: Aβ, amyloid-β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Results

Clinical efficacy of the two groups

The ORR was 91.0% in the research group, which was significantly higher than that of 79.9% in the control group (P<0.05, **Table 2**).

Serum Aβ1-40, Aβ1-42, IL-6 and TNF-α levels in the two groups

The serum Aβ1-40, Aβ1-42, IL-6 and TNF-α levels showed no significant difference between the two groups before treatment (P>0.05). At 2 h, 24 h and 7 d after treatment, serum Aβ1-40 increased, and was higher in the research group compared with the control group at each time point (P<0.05, **Figure 1A**). At 2 h, 24 h and 7 d after treatment, serum Aβ1-42 in the research group increased and began to decrease 7 d after treatment, while serum Aβ1-42 in the control group continued to decrease within 14 d after treatment; however, serum Aβ1-42 in the research group was higher than that in the control group at each time point after treatment (P<0.05, **Figure 1B**). At 2 h, 24 h and 7 d after treatment, serum IL-6 in the control group increased; whilst serum IL-6 in the research group decreased after 24 h, and was higher within 24 h after treatment but lower from 24 h onward compared with the control group (P<0.05, **Figure 1C**). Within 2 hours after treatment, serum TNF-α in the research group showed a downward trend, which slightly increased from 2 h to 24 h and decreased again after 24 h. In the control group, serum TNF-α showed a downward trend within 2 h after treatment and gradually increased since then. Serum TNF-α in the research group was lower than that in the control group at 24 h, 7 d and 14 d after treatment (P<0.05, **Figure 1D**).

NIHSS scores of two groups

The NIHSS score differed insignificantly between the two groups before treatment (P>0.05). After treatment, the NIHSS score showed a downward trend in both groups, and the score in the research group at 2 h, 24 h, 7

Table 3. Comparison of NIHSS scores between the two groups

	Before treatment	2 hours after treatment	24 hours after treatment	7 days after treatment	14 days after treatment
Control group (n=69)	23.64±3.15	19.26±2.41	17.67±2.83	14.67±2.11	11.68±2.84
Research group (n=100)	22.97±3.37	17.54±2.81	14.32±2.06	8.67±2.29	6.48±2.97
χ^2/t	1.3043	4.1404	8.9060	17.2814	11.3877
P	0.1939	<0.0001	<0.0001	<0.0001	<0.0001

Note: NIHSS: National Institutes of Health Stroke Scale.

Table 4. Comparison of MMSE and MoCA scores between the two groups

	MMSE score			MoCA score		
	Before treatment	30 days after treatment	90 days after treatment	Before treatment	30 days after treatment	90 d after treatment
Control group (n=69)	16.84±2.67	19.97±1.37	23.54±1.79	16.54±1.84	20.58±2.14	22.06±1.62
Research group (n=100)	17.15±3.06	22.64±2.16	27.68±1.87	16.49±2.03	23.84±1.97	26.87±2.28
χ^2/t	0.6813	9.0803	14.3937	0.1634	10.2063	15.0864
P	0.4966	<0.0001	<0.0001	0.8704	<0.0001	<0.0001

Note: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

Table 5. Comparison of mRS scores between the two groups

	Before treatment	30 days after treatment	90 days after treatment
Control group (n=69)	4.26±0.37	3.12±0.33	2.57±0.21
Research group (n=100)	4.35±0.41	2.67±0.23	2.06±0.19
χ^2/t	1.4588	10.4505	16.4262
P	0.1465	<0.0001	<0.0001

Note: mRS, Modified Rankin Scale.

d and 14 d after treatment was significantly lower than that in the control group (P<0.05, **Table 3**).

MMSE and MoCA scores of the two groups

The MMSE and MoCA scores were not significantly different between the two groups before treatment (P>0.05). On the 30th and 90th day after treatment, MMSE and MoCA scores showed an upward trend in both groups and were both higher in the research group compared with the control group (P<0.05, **Table 4**).

mRS scores of the two groups

There was no significant difference in the mRS score between the two groups before treatment (P>0.05). After 30 days and 90 days of treatment, the mRS score showed a downward trend in both groups and was lower in the research group compared with the control group (P<0.05, **Table 5**).

Incidence of adverse reactions in the two groups

In the control group, there were 3 cases of encephalorrhagia, 5 cases of vascular re-occlusion, 2 cases of ischemia-reperfusion injury, 4 cases of cerebral vasospasm, 7 cases of severe headache and 36 cases of cognitive dysfunction. In the research group, encephalorrhagia was observed in 2 cases, vascular re-occlusion in 2 cases, ischemia-reperfusion injury in 5 cases, cerebral vasospasm in 5 cases, severe headache in 5 cases and cognitive dysfunction in 15 cases. No significant difference was observed in the incidence of adverse reactions between the two groups other than the incidence of cognitive dysfunction and the total incidence (P<0.05, **Table 6**).

Discussion

Previous studies have shown that when hemodynamic disturbance occurs in the brain, the metabolism of proteins, lipids and nucleic acids, which are the main components of cells and tissues, will be affected due to the blocked blood circulation and ischemia and hypoxia of local brain tissues; moreover, hemodynamic disturbance will impair BBB function and change its permeability [18, 19]. When

Table 6. Comparison of adverse reactions between the two groups

	Encephalorrhagia	Blood vessel re-occlusion	Ischemia-reperfusion injury	Cerebral vasospasm	Severe headache	Cognitive dysfunction	Total incidence of adverse reactions
Control group (n=69)	3 (4.3)	5 (7.2)	2 (2.9)	4 (5.8)	7 (10.1)	36 (52.2)	47 (68.1)
Research group (n=100)	2 (2.0)	2 (2.0)	5 (5.0)	5 (5.0)	5 (5.0)	15 (15.0)	33 (33.0)
χ^2/t	0.7839	2.8301	0.4541	0.0515	1.6381	26.7810	20.2010
P	0.3760	0.0925	0.5004	0.8206	0.2005	<0.0001	<0.0001

ischemia and hypoxia exceed a certain time limit, the above hazards will be further amplified, resulting in permanent inactivation of neurons and glial cells, as well as the worsening symptoms of neurological deficits such as cognitive impairment [20]. In patients with ACI, the high-risk tissue of ischemic edema zone around the infarct site can be rescued under certain conditions when the symptoms begin to appear, and rapid and effective recanalization of infarcted blood vessels can greatly ameliorate the sequelae of treatment [21]. Mechanical thrombectomy of cerebral artery is one of the means to relieve hemodynamic disturbance. Under the guidance of digital subtraction angiography, retrievable stents or thrombus aspirators are delivered to the cerebrovascular stenosis site through intravascular interventional technique to remove thrombus and realize rapid recanalization of the occluded vessels [22].

In this study, it was found that serum Aβ1-40, Aβ1-42, IL-6 and TNF-α levels showed significant difference between the two groups at 7 and 14 days after thrombectomy, and the NIHSS, MMSE and MoCA scores were obviously better in the research group compared with the control group. Aβ is a metabolite of amyloid precursor protein (APP), whose production and clearance are dynamically balanced under normal circumstances [17]. And under physiological conditions, Aβ is a soluble substance that can be excreted from the body with the circulation of body fluids such as cerebrospinal fluid and peripheral blood [23]. Hemodynamic obstacles lead to increased Aβ production and blocked clearance [24]. The data of this research showed that Aβ1-40 increased rapidly within 2 h after thrombectomy, continued to increase from 2 h to 7 days, and gradually leveled off from day 7 to 14; while serum Aβ1-42 in patients undergoing thrombectomy was higher than that in the control group at all time points after treatment. After 90 days of follow-up, the incidence of cognitive impairment was found to be much lower in the research group treated by thrombectomy.

Relevant studies [25, 26] revealed that when ACI occurred, local CBF was blocked and cerebral ischemia and hypoxia promoted excessive APP production, at which time, APP was more abnormally cleaved through the amyloid degradation pathway, resulting in the high production state of Aβ1-40 due to the excessive raw materials and the increased production pathways. After mechanical thrombectomy, the hemodynamic barrier was lifted, and the hyperproduction state of Aβ1-40 caused by hypoxia and ischemia was eliminated. Therefore, the increase of Aβ1-40 slowed down when it rose to a certain level, and the vasoconstriction effect of Aβ1-40 on cerebral vessels and the toxic effect of neuronal cells were weakened accordingly. In addition, compared with those with impaired CBF, the effective clearance of Aβ1-40 by the body in those with unobstructed CBF, as well as the repair of BBB and the preservation of microglia function allow for effective protection of the cognitive function. Oliver et al. [27] found that peripheral blood Aβ1-42 level was significantly lower than the reference range in patients with cognitive impairment. The possible reason is that Aβ1-42 tends to accumulate and precipitate to form plaques in the brain, which leads to the increase of Aβ1-42 deposited in senile plaques in brain parenchyma and the decrease of Aβ1-42 transported to the soluble state in peripheral blood. In the current research, serum Aβ1-42 concentration in the research group remained at a high level within 7 days after thrombectomy, and although it decreased in 7-14 days, it was still evidently higher than that in the control group. It suggests that when CBF is obstructed, Aβ1-42 is likely to be blocked and prone to remain in the brain parenchyma, and the relief of hemodynamic disorder helps Aβ1-42 to be released to the periphery, which is conducive to

the reduction of Aβ1-42 deposition in the brain parenchyma.

Furthermore, we explored the changes of serum IL-6 and TNF-α levels in patients. IL-6 is a common interleukin-like inflammatory factor, which increases rapidly in the event of acute inflammation and tissue injury, and will quickly recover to physiological level in a short time with the release of stress [28]. It has been reported in the literature [29] that high IL-6 levels can lead to cognitive disorders such as vascular dementia, and the inflammatory reaction mediated by it is a common inducement for the occurrence and development of dementia. In this study, the IL-6 level in the research group was higher than that in the control group at 2 h and 24 h, but was subsequently markedly lower than that in the control group, indicating that the blood supply recovery after thrombolectomy did not show a role in dissipating the inflammatory response at the early stage of treatment, which may be related to ischemia-reperfusion injury. TNF-α, a common cytokine, can promote inflammation, induce the release of inflammatory cytokines and promote cell necrosis [30]. Relevant data have shown that higher than normal levels of TNF-α can be detected in the central nervous system of people with cognitive impairment, and TNF-α can damage nerve cells by inducing inflammatory response [31]. The data of this study showed that the TNF-α level in the research group began to decrease within 2 h after thrombectomy, and increased from 2 h to 24 h; however, it showed a downward trend at 24 h-14 d and was distinctly lower than that in the control group. A study suggests that [32], serum TNF-α appears to show a short-term decrease in the early stage of cerebral infarction thrombectomy, which may be due to the aggregation of TNF-α to the damaged cerebral vessels to chemoattract phagocyte in the early stage of acute inflammation, so the level measured from peripheral blood is on the low side. With the progression of inflammation, a large number of inflammation-related factors such as IL-6 are released, which reversely stimulates TNF-α to increase its secretion, so the TNF-α level measured from the peripheral blood begins to rise. Based on cognitive function, intelligence, and neurological function scores, we found that thrombectomy had a protective effect on long-term cognitive function.

Although this study has obtained encouraging results, it still has several limitations. The retrospective nature of analysis does not allow randomization of patients in either group so that the similarity of patients in groups is jeopardized. Therefore, a well-designed, randomized and controlled trial with prospective data collection is needed to confirm the findings of our study.

To sum up, with a high safety profile, cerebral artery thrombectomy has a definite effect on patients with ACI, which can effectively relieve the hemodynamic disorders, reduce the neurotoxicity of Aβ and inhibit inflammation, thus playing a certain role in cognitive function preservation. This study is expected to provide a new way to focus on suppressing inflammation or other pathologic events, which could offer new hope for the prevention and treatment of ACI.

Disclosure of conflict of interest

None.

Address correspondence to: Zengjun Wang and Liandong Zhao, Department of Neurology, Xuzhou Medical University Affiliated Hospital of Huai'an, No. 62, Huaihai South Road, Huai'an 223002, Jiangsu Province, China. Tel: +86-0517-80871636; E-mail: zjwang126@126.com (ZJW); Tel: +86-18124223-405; E-mail: liandong_zhao@163.com (LDZ)

References

[1] Sveinsson OA, Kjartansson O and Valdimarsson EM. Cerebral ischemia/infarction-diagnosis and treatment. Laeknabladid 2014; 100: 393-401.

[2] Novotny V, Khanevski AN, Bjerkreim AT, Kvistad CE, Fromm A, Waje-Andreassen U, Næss H, Thomassen L and Logallo N. Short-term outcome and in-hospital complications after acute cerebral infarcts in multiple arterial territories. Stroke 2019; 50: 3625-3627.

[3] Sun Z, Xu Q, Gao G, Zhao M and Sun C. Clinical observation in edaravone treatment for acute cerebral infarction. Niger J Clin Pract 2019; 22: 1324-1327.

[4] Heit JJ, Zaharchuk G and Wintermark M. Advanced neuroimaging of acute ischemic stroke: penumbra and collateral assessment. Neuroimaging Clin N Am 2018; 28: 585-597.

[5] Farokhi-Sisakht F, Farhoudi M, Sadigh-Eteghad S, Mahmoudi J and Mohaddes G. Cognitive rehabilitation improves ischemic stroke-induced

cognitive impairment: role of growth factors. J Stroke Cerebrovasc Dis 2019; 28: 104299.
[6] Yang YM, Zhao ZM, Wang W, Dong FM, Wang PP, Jia YJ, Han N, Jia YL and Wang JH. Trends in cognitive function assessed by a battery of neuropsychological tests after mild acute ischemic stroke. J Stroke Cerebrovasc Dis 2020; 29: 104887.
[7] Bill O, Inácio N, Lambrou D, Wintermark M, Ntaios G, Dunet V and Michel P. Focal hypoperfusion in acute ischemic stroke perfusion CT: clinical and radiologic predictors and accuracy for infarct prediction. AJNR Am J Neuroradiol 2019; 40: 483-489.
[8] Sun MS, Jin H, Sun X, Huang S, Zhang FL, Guo ZN and Yang Y. Free radical damage in ischemia-reperfusion injury: an obstacle in acute ischemic stroke after revascularization therapy. Oxid Med Cell Longev 2018; 2018: 3804979.
[9] Brugnara G, Neuberger U, Mahmutoglu MA, Foltyn M, Herweh C, Nagel S, Schönenberger S, Heiland S, Ulfert C, Ringleb PA, Bendszus M, Möhlenbruch MA, Pfaff JAR and Vollmuth P. Multimodal predictive modeling of endovascular treatment outcome for acute ischemic stroke using machine-learning. Stroke 2020; 51: 3541-3551.
[10] Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA and Davis SM; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015; 372: 1009-1018.
[11] Gao Y, Song Y, Yin X, Wu W, Zhang L, Chen Y and Shi W. Deep learning-based digital subtraction angiography image generation. Int J Comput Assist Radiol Surg 2019; 14: 1775-1784.
[12] Lee SJ, Liu B, Rane N, Mitchell P, Dowling R and Yan B. Correlation between CT angiography and digital subtraction angiography in acute ischemic strokes. Clin Neurol Neurosurg 2021; 200: 106399.
[13] Wiesmann M, Kalder J, Reich A, Dekeyzer S, Riabikin A, Mpotsaris A and Nikoubashman O. Combined surgical and endovascular carotid access for endovascular thrombectomy in acute ischemic stroke. World Neurosurg 2019; 132: e1-e4.
[14] Seitz DP, Gill SS, Austin PC, Bell CM, Anderson GM, Gruneir A and Rochon PA. Rehabilitation of older adults with dementia after hip fracture. J Am Geriatr Soc 2016; 64: 47-54.
[15] Chang R, Knox J, Chang J, Derbedrossian A, Vasilevko V, Cribbs D, Boado RJ, Pardridge WM and Sumbria RK. Blood-brain barrier penetrating biologic TNF-α inhibitor for Alzheimer's disease. Mol Pharm 2017; 14: 2340-2349.
[16] Nyúl-Tóth Á, Tarantini S, DelFavero J, Yan F, Balasubramanian P, Yabluchanskiy A, Ahire C, Kiss T, Csipo T, Lipecz A, Farkas AE, Wilhelm I, Krizbai IA, Tang Q, Csiszar A and Ungvari Z. Demonstration of age-related blood-brain barrier disruption and cerebromicrovascular rarefaction in mice by longitudinal intravital two-photon microscopy and optical coherence tomography. Am J Physiol Heart Circ Physiol 2021; 320: H1370-H1392.
[17] Wang X, Zhou X, Li G, Zhang Y, Wu Y and Song W. Modifications and trafficking of APP in the pathogenesis of Alzheimer's disease. Front Mol Neurosci 2017; 10: 294.
[18] Porebska A, Nowacki P, Safranow K and Nowik M. Hemodynamic blood flow disturbances in the middle cerebral arteries in patients with atrial fibrillation during acute ischemic stroke. Clin Neurol Neurosurg 2008; 110: 434-440.
[19] Doubovikov ED and Aksenov DP. Oscillations and concentration dynamics of brain tissue oxygen in neonates and adults. J Comput Neurosci 2020; 48: 21-26.
[20] Bayat M, Zabihi S, Karbalaei N and Haghani M. Time-dependent effects of platelet-rich plasma on the memory and hippocampal synaptic plasticity impairment in vascular dementia induced by chronic cerebral hypoperfusion. Brain Res Bull 2020; 164: 299-306.
[21] Hu H, Yan S, Zhou Y and Lou M. Time-dependent infarct volume affects the benefit of recanalization. Neuroimage Clin 2019; 24: 102000.
[22] Zenych A, Fournier L and Chauvierre C. Nanomedicine progress in thrombolytic therapy. Biomaterials 2020; 258: 120297.
[23] Lee SJC, Nam E, Lee HJ, Savelieff MG and Lim MH. Towards an understanding of amyloid-β oligomers: characterization, toxicity mechanisms, and inhibitors. Chem Soc Rev 2017; 46: 310-323.
[24] Yang J, d'Esterre CD, Amtul Z, Cechetto DF and Lee TY. Hemodynamic effects of combined focal cerebral ischemia and amyloid protein toxicity in a rat model: a functional CT study. PLoS One 2014; 9: e100575.
[25] Hartz AM, Bauer B, Soldner EL, Wolf A, Boy S, Backhaus R, Mihaljevic I, Bogdahn U, Klünemann HH, Schuierer G and Schlachetzki F. Amyloid-β contributes to blood-brain barrier leakage in transgenic human amyloid precur-

sor protein mice and in humans with cerebral amyloid angiopathy. Stroke 2012; 43: 514-523.

[26] Koenig LN, McCue LM, Grant E, Massoumzadeh P, Roe CM, Xiong C, Moulder KL, Wang L, Zazulia AR, Kelly P, Clesham GJ and Karamasis GV. Lack of association between acute stroke, post-stroke dementia, race, and β-amyloid status. Neuroimage Clin 2021; 29: 102553.

[27] Hanon O, Vidal JS, Lehmann S, Bombois S, Allinquant B, Tréluyer JM, Gelé P, Delmaire C, Blanc F, Mangin JF, Buée L, Touchon J, Hugon J, Vellas B, Galbrun E, Benetos A, Berrut G, Paillaud E, Wallon D, Castelnovo G, Volpe-Gillot L, Paccalin M, Robert PH, Godefroy O, Dantoine T, Camus V, Belmin J, Vandel P, Novella JL, Duron E, Rigaud AS, Schraen-Maschke S and Gabelle A; BALTAZAR study group. Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers. Alzheimers Dement 2018; 14: 858-868.

[28] Unver N and McAllister F. IL-6 family cytokines: key inflammatory mediators as biomarkers and potential therapeutic targets. Cytokine Growth Factor Rev 2018; 41: 10-17.

[29] Miwa K, Okazaki S, Sakaguchi M, Mochizuki H and Kitagawa K. Interleukin-6, interleukin-6 receptor gene variant, small-vessel disease and incident dementia. Eur J Neurol 2016; 23: 656-663.

[30] Chen AQ, Fang Z, Chen XL, Yang S, Zhou YF, Mao L, Xia YP, Jin HJ, Li YN, You MF, Wang XX, Lei H, He QW and Hu B. Microglia-derived TNF-α mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. Cell Death Dis 2019; 10: 487.

[31] Decourt B, Lahiri DK and Sabbagh MN. Targeting tumor necrosis factor alpha for Alzheimer's disease. Curr Alzheimer Res 2017; 14: 412-425.

[32] Wytrykowska A, Prosba-Mackiewicz M and Nyka WM. IL-1β, TNF-α, and IL-6 levels in gingival fluid and serum of patients with ischemic stroke. J Oral Sci 2016; 58: 509-513.