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Clinical treatment efficiency of mechanical thrombectomy combined with rhPro-UK thrombolysis for acute moderate/severe cerebral infarction

Q.-S. ZHAO[1], W. LI[2], D. LI[1], T. LIU[1], J.-H. WANG[1], Y. GAO[1], L. YI[1], R.-K. ZHAO[1]

[1]Department of Stroke Ward, Affiliated Hospital of Beihua University, Jilin City, Jilin Province, China
[2]Department of Neurology A Therapeutic Area, Affiliated Hospital of Beihua University, Jilin City, Jilin Province, China

Abstract. – OBJECTIVE: This study aims to compare clinical efficiency of mechanical thrombectomy combined with rhPro-UK thrombolysis on moderate or severe acute brain infarction.

PATIENTS AND METHODS: A total of 90 acute cerebral infarction patients due to artery stenosis or blockade from May 2016 to May 2017 were recruited and randomly assigned into thrombolysis group (N = 30), mechanical thrombectomy (N = 30), and combined treatment group (N = 30). Clinical information was collected. Thrombolysis group received rhPro-UK, mechanical thrombectomy group received Solitaire scaffold, and combined group received rhPro-UK after Solitaire scaffold. Barthel scale and NIHSS scale were used to evaluate the quality of life and mental deficit of patients. Modified thrombolysis in cerebral infarction (mTICI) was compared among three groups, along with the observation of hemorrhage, neurological recovery within 90 days, and adverse effects.

RESULTS: No significant difference was found in NIHSS within 24 h of treatment among three groups ($p > 0.05$), but the decreasing levels were shown at 24 h, 7 days, and 90 days comparing to those before treatment ($p < 0.05$). In combined treatment group, lower NIHSS at 7 d and 90 d were detected comparing to other two groups ($p < 0.05$). Recanalization rates were 53.33% and 60.00% in thrombolysis and mechanical groups ($p > 0.05$), respectively, which were significantly lower than that in combined group (83.33%) ($p < 0.05$). Curative rate in combined group was 70%, significantly higher than thrombolysis (46.67%) and mechanical group (53.33%) ($p < 0.05$). No statistical difference of curative rate was observed between thrombolysis and mechanical groups ($p > 0.05$). Moreover, neither significant difference of coagulation function nor platelet count was found among three groups ($p > 0.05$).

CONCLUSIONS: Mechanical thrombectomy combined with thrombolysis presented favorable efficiency in the treatment of moderate to severe acute cerebral infarction than single treatment, among which the occurrences of adverse effects were similar.

Key Words:
Mechanical thrombectomy, Arterial thrombolysis, rhPro-UK, Cerebral infarction.

Introduction

Acute cerebral infarction (ACI) represents a commonly occurred cerebral vascular disease, with relatively high incidence, mortality, and morbidity rates. It emerges as the main pathogenic factors in adults, severely threatens health-related quality of life of patients, and causes major burden for the family and public[1,2]. Thrombolysis is one of the most effective approaches in the therapy of ACI as it can recanalize blocked vessels timely, regain blood perfusion in ischemic region, and maximally decrease irreversible damage of brain tissues[3,4]. Even though, the successful rate of thrombolysis in clinics is still relatively low. In developed countries, the effective rate of thrombolysis is only 11.6%-60.0% based on statistics, and such figure is even lower in China[5].

Currently applicable thrombolysis approaches include venous thrombolytic drug infusion, artery mechanical thrombectomy, and combined thrombolysis[6]. Diagnosis and treatment guideline for ACI of China (year 2014) stipulated venous thrombolysis as primary recommended

Corresponding Author: Qingshi Zhao, MD; e-mail: gu00008042@163.com

treatment. However, relatively drawback still exists in the therapy such as short time window (3-4.5h). Moreover, venous thrombolysis leads to various complications, including lower local drug concentration at thrombolysis lesion, high drug dosage, thrombolysis-induced hemorrhage[7]. Arterial thrombolysis extends the time window to 6 h, exhibits significant advantages over venous thrombolysis, and thus becomes a popular approach for ACI treatment in clinics. Arterial thrombolysis shows excellent control in the management of dosage of thrombolytic drugs and local blood drug concentration at thrombosis lesion site, thus it improves recanalization rate of blockade vessels, and decreases the incidence of complications such as hemorrhage[8]. A study[5] showed that although thrombolytic rate of arterial thrombolysis can be improved to about 50%, the rate of thrombolysis failure still nearly reaches 50%. Current researches focus on combination of two or more thrombolytic approaches, including arterial-venous thrombolysis combination, artery thrombolysis with mechanical thrombectomy, balloon dilated angioplasty, and scaffold implantation, in order to shorten recanalization time, improve recanalization rate and patient prognosis[9]. Mechanical thrombolysis has enhancing effects on blockade of major arteries, whilst arterial thrombolysis exerts satisfactory function on relatively smaller thrombosis. It has been proposed[10] that mechanical combined with arterial thrombolysis can increase the successful rate and shorten thrombolysis duration. This study investigated the clinical efficiency and feasibility of mechanical thrombectomy combined with recombinant human pro-urine kinase (rhPro-UK) for arterial thrombolysis among ACI patients.

Patients and Methods

Patients

A total of 90 moderate or severe ACI patients caused by major artery stenosis or blockade from May 2016 to May 2017 were recruited, including 62 males and 28 females, aging between 49 and 78 years (average = 58.67 ± 13.07 years). Patients were randomly assigned into arterial thrombolysis group, mechanical thrombectomy, and combined treatment groups (N = 30 each). In the arterial thrombolysis group, there were 22 males and 8 females, aging between 49 and 77 years (average = 58.13 ± 12.76 years). The average time duration of treatment was 4.82±2.61h. In this group, there were 8 hypertension patients, 6 diabetic patients, and 3 individuals with coronary heart disease. In the mechanical thrombectomy group, there were 21 males and 9 females, aging between 50 and 74 years (average = 57.81 ± 11.53 years). The average time duration of treatment was 4.25 ± 2.84 h. In this group, there were 7 hypertension patients, 5 diabetic patients, and 5 individuals with coronary heart disease. In the combined treatment group, there were 19 males and 11 females, aging between 52 and 78 years (average = 58.87 ± 13.69 years). The average time duration was 4.58 ± 2.45 h. In this group, there were 7 hypertension patients, 7 diabetic patients, and 4 individuals with coronary heart disease. No significant difference was shown in sex, age, time duration since disease onset toward treatment, and incidence of complications among three groups of patients ($p > 0.05$). All patients accorded with ACI diagnosis guideline modified by 4th National Cerebrovascular Disease Conference. All patients aged between 18 and 80 years, without hemorrhage by head CT, or early signs of major cerebral infarction signals. Those patients with previous history of intracranial hemorrhage, major head trauma or surgery within 3 months, brain ischemia or myocardial infarction history, or complicated with severe dysfunction of heart, lung, kidney or liver, or those malignant tumor, severe diabetes or complications patients were excluded. Other patients who take anticoagulants, anti-platelet drugs or fibrinolysis drugs, or those who refuse to comply with treatment were excluded. The Ethical Committee of our hospital approved this study. All the patients signed the informed consents.

General Methods

All patients received routine dehydration and intracranial pressure depression treatment, along with brain protection and symptomatic measures. Head CT scanning was performed to rule out hemorrhage and low-density lesions. Head CT angiography (CTA) or magnetic resonance angiography (MRA) was used to confirm vessel blockade. Some patients also received diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) to confirm ischemia dark bands. After pre-op examination was completed, patients were sent to invention therapy center for DSA to confirm vessel condition followed by thrombolysis treatment.

Single rhPro-UK Arterial Thrombolysis

Patients lay in supine position, and received routine nursing and sterilization. Local anesthesia was performed at the site of arterial puncture, followed by systemic heparinization. Seldinger approach was used for unilateral femoral artery puncture, and 6F cannula sheath was implanted. 6F-guiding head was placed into the internal carotid artery. DSA (using 300 mg/mL contrast agent) was performed to conclude vascular blockade site. Under DSA guide, micro-cannula (Echelon-14) was placed into the proximal site of blockade vessel, and 200 000 U rhPro-UK was dissolved into 20 mL saline, which was infused at 20 000 U/min velocity. DSA was performed to observe the recanalization of vessels. Within 10-15 min, angiography was performed once, and a second drug infusion was performed if no recanalization occurred. During surgery, additional rhPro-UK may be applied depending on the thrombolysis condition, under the maximal dosage of 750 000 U. After infusion, the cannula was retracted, followed by skin sterilization and stitching.

Mechanical Thrombectomy by Solitaire Scaffold

DSA was performed to identify vascular blockade site as described in arterial thrombolysis section. After confirmation of vascular blockade site, roadmap guidance was used to locate retriever (Stryker head) into thrombosis site with a guidewire. After scaffold system was released for 5 min, it was retracted. DSA was used to observe recanalization, and repeated procedures were performed if no recanalization was observed for at least three times. The cannula was retracted, followed by sterilization and stitching.

Mechanical Thrombectomy Combined With rhPro-UK Arterial Thrombolysis

Using DSA, the site of thrombolysis was identified as previously described. Mechanical thrombectomy was firstly performed, followed by infusion of 200 000 U rhPro-UK for arterial thrombolysis. The treatment was terminated if vascular recanalization was observed. Repeated procedures can be performed for at most three times if no recanalization occurred. During surgery, rhPro-UK was replenished with maximal dosage at 750 000 U depending on thrombolysis condition.

Post-Thrombolysis Treatment

Head CT or MRI was performed within 24 h of thrombolysis treatment. If no brain hemorrhage occurred, 100 mg/d aspirin tablet was applied, with subcutaneous injection of low molecular heparin (5 000 U, twice daily). Intracranial pressure was depressed, while symptomatic treatment such as anti-free radicals, neural nutrients, blood pressure control, blood glucose and nutrient support was performed. Patient recovery was managed by rehabilitation therapy and exercise for functional recovery.

Observation Indexes

General Information

Before thrombolysis, at 24 h and 7 d after treatment, blood and urine examinations were performed for the measurement of platelet count, blood glucose, liver/kidney function, electrical cardiogram, and coagulation function assay. Head CT scan was conducted before and at 24 h after thrombolysis.

Neurological Dysfunction Scale

NHISS was used for evaluation[11] before and at 24 h, 7 d, and 90 d after treatment. Within a 0-28 points scale, higher score indicated worse recovery of neurological functions, and vice versa.

Evaluation of Vascular Recanalization

The improved scale of cerebral infarction thrombolysis mTICI was used for evaluation[12]. Grade 0-2a was assigned as ineffective, grade 2b indicated effective, and grade 3 referred to significant efficiency.

Treatment Efficiency Evaluation

At 90 d after treatment, improved Rankin scale (mRs) was used to evaluate patient prognosis. mRS less than 2 points indicated satisfactory prognosis, and between 3 and 6 points meant unfavorable prognosis. The occurrence of complication was recorded, including secondary hemorrhage, intracranial infection, and late onset hydrocephalus.

Statistical Analysis

SPSS 18.0 (SPSS Inc., Released 2009. PASW Statistics for Windows, Chicago, IL, USA) was used to generate a database for statistical analysis. Measurement data were presented as mean±standard deviation (SD). *F*-test was used for comparison among three groups. LSD test was used in comparison between two groups. Enumeration

Table I. NIHSS scores among three groups of patients before and after treatment.

	Before treatment	24 h	7 d	90 d
Arterial thrombolysis	14.52 ± 6.08	11.07 ± 8.26	5.57 ± 5.83[a]	4.26 ± 2.37[a]
Mechanical thrombectomy	13.74 ± 5.83	11.72 ± 8.94	5.68 ± 5.27[a]	4.42 ± 2.18[a]
Combined treatment	14.26 ± 5.15	10.69 ± 9.05	4.35 ± 5.08[a,b,c]	3.7 ± 2.24[a,b,c]

Note: [a]$p < 0.05$ comparing to before treatment; [b]$p < 0.05$ comparing to arterial thrombolysis group; [c]$p < 0.05$ comparing to mechanical thrombectomy group.

data were presented as ratio or percentage. Chi-square analysis was then performed. A statistical significance was defined when $p < 0.05$.

Results

Comparison of NIHSS Score Among Three Groups of Patients

No significant difference of NIHSS score was observed among three groups before and 24h after treatment ($p > 0.05$). Compared to NIHSS score before treatment, it significantly decreased among all three groups of patients at 24 h, 7 d, and 90 d after treatment ($p < 0.05$). Of note, the NIHSS scores from combined treatment group at 7 d and 90 d post-treatment were significantly reduced compared to that in mechanical thrombectomy and arterial thrombolysis groups, correspondingly ($p < 0.05$, Table I).

Vascular Recanalization Condition Analysis

Our data on vascular recanalization showed that the rates were 53.33% and 60.00% in arterial thrombolysis and mechanical thrombectomy groups, respectively ($p > 0.05$). However, the recanalization rate was 83.33% in combined treatment group, which was significantly higher than that in arterial thrombolysis or mechanical thrombectomy groups ($p < 0.05$, Table II).

Treatment Efficiency Among Three Groups of Patients

Overall curative rate was 70% in combined treatment group at day 90, significantly higher than that arterial thrombolysis group (46.67%) and mechanical thrombectomy group (53.33%) ($p < 0.05$). Nevertheless, no significant difference was found in curative rate between arterial thrombolysis and mechanical thrombectomy group ($p > 0.05$, Table III).

Comparison of Blood Coagulation Function and Platelet Count Among Three Groups of Patients

No significant difference coagulation and platelet count was detected among three groups of patients before, at 24 h and 7 d after treatment ($p > 0.05$ Table IV).

Table II. Vascular recanalization condition among three groups.

	Ineffective (N)	Effective (N)	Significant (N)	Recanalization (%)
Arterial thrombolysis	14 (46.67)	11 (36.67)	5 (16.67)	16 (53.33)
Mechanical thrombectomy	12 (40.00)	12 (40.00)	6 (30.00)	18 (60.00)
Combined treatment	5 (16.67)	14 (46.67)	11 (36.67)	25 (83.33)[a,b]

Note: [a]$p < 0.05$ comparing to arterial thrombolysis group; [b]$p < 0.05$ comparing to mechanical thrombectomy group.

Table III. Comparison of 90d treatment efficiency among three groups of patients.

	mRs ≤ 2	3 ≤ mRs ≤ 6	90d curative rate (%)
Arterial thrombolysis	14 (46.67)	16 (53.33)	14 (46.67)
Mechanical thrombectomy	16 (53.33)	14 (46.67)	16 (53.33)
Combined treatment	21 (70.00)	9 (30.00)	21 (70.00)[a,b]

Note: [a]$p < 0.05$ comparing to arterial thrombolysis group; [b]$p < 0.05$ comparing to mechanical thrombectomy group.

Table IV. Comparison of blood coagulation and platelet count among three groups.

	Arterial thrombolysis			Mechanical thrombectomy			Combined treatment		
	Before	24 h	7 d	Before	24 h	7 d	Before	24 h	7 d
APTT (s)	14.93 ± 2.58	20.13 ± 3.07	16.27 ± 2.86	15.48 ± 2.74	20.75 ± 3.11	16.82 ± 3.04	16.07 ± 2.95	21.23 ± 3.31	17.46 ± 2.77
FIB (g/L)	3.55 ± 0.97	3.29 ± 1.24	3.86 ± 2.31	3.48 ± 1.36	3.17 ± 1.92	3.79 ± 2.17	3.64 ± 1.13	3.08 ± 1.85	4.02 ± 2.24
PT (s)	11.78 ± 2.34	12. 63 ± 1.52	12.15 ± 1.73	11.81 ± 1.94	12.46 ± 2.03	11.93 ± 1.47	11.69 ± 2.41	12.17 ± 1.36	11.71 ± 1.58
PLT ($\times 10^9$/L)	201.82 ± 52.23	200.94 ± 53.48	204.57 ± 52.14	200.71 ± 50.96	201.42 ± 51.57	203.05 ± 51.02	202.11 ± 51.87	201.48 ± 52.16	204.83 ± 51.71

Occurrence of Complications Among Three Different

No death was found among all patients. In arterial thrombolysis group, there were 3 cases of secondary hemorrhage, 2 individuals with hypotension, and 1 cases of coagulation dysfunction, with overall adverse rates of 20.00%. In mechanical thrombectomy group, there were 4 cases of secondary hemorrhage, 1 case with hypotension, and 2 cases of re-thrombosis of blood vessels, with overall adverse rates of 23.33%. Furthermore, in combined treatment group, there were 2 cases of secondary hemorrhage, 2 cases with coagulation dysfunction, and 1 cases of re-thrombosis of blood vessels, with overall adverse rates of 16.67%. No significant difference of adverse effects existed among three groups ($p > 0.05$).

Discussion

ACI is a type of cerebrovascular disease with high incidence, morbidity, and mortality, which is mainly caused by irreversible damage of brain nerves after cerebral arterial vessel blockade by thrombosis. Therefore, early recanalization of blocked brain vessels is generally employed to regain brain blood infusion effectively. Therefore, the keystone for ACI treatment is the alleviation of ischemia brain damage[13]. Currently the most widely used and effective method for treating ACI is thrombolysis, which mainly consists of venous thrombolysis, arterial thrombolysis, and mechanical thrombectomy. However, it is still controversial for clinicians during the practical use due to the diverse disadvantages[14]. The application of venous thrombolysis is largely limited accounting for short time window within 3h, leading to frequent loss of optimal treatment time, and relatively lower recanalization rate of vessels[7].

Arterial thrombolysis is gradually developed by wide application of intervention therapy approach in clinics. It can extend the treatment time window to 6h, largely improving effective rate[15]. Moreover, DSA guided arterial thrombolysis can directly release drugs toward the vessel thrombosis site, facilitating the increase of local drug concentration at thrombosis site. It thus benefits the decrease of drug dosage, improves recanalization rate of blockade vessels, shortens recanalization time, and reduces incidence of hemorrhage or other complications[16]. A previous study[15] showed that arterial thrombolysis could increase vessel recanalization rate to about 50%. In this study, we found that recanalization rate of arterial thrombolysis group reached 53.33%, which was in consistent with the previous study. Arterial thrombolysis effectively improves recanalization rate, but the rate of ineffective treatment remains to be nearly 50%. Therefore, recent reports tried to combine mechanical thrombectomy along with arterial thrombolysis, in order to elevate recanalization rate of blocked vessels[17].

Mechanical thrombectomy mainly targets large artery thrombosis, and requires a short time to regain blood flow. However, mechanical thrombectomy may produce mini-thrombosis, resulting in the increasing rate of secondary vascular thrombosis[18]. Multiple thrombectomy apparatuses including Merci, Solitaire scaffold, and Penumbra system have been developed. Saver et al[19] analyzed the effectiveness of mechanical thrombectomy and 61% recanalization rate was retained using Solitaire scaffold treating ACI, but only 24% recanalization rate was obtained with Merci. This work employed Solitaire scaffold for thrombectomy, and we found 60% recanalization rate, which was similar to the findings of Saver et al[19].

Combination of mechanical thrombectomy and arterial thrombolysis has become newly emerged as hotspots for research[20]. Under DSA guidance, thrombolysis drug was injected at the lesion site, simultaneously with mechanical rupture. The combination of these two approaches can markedly decrease thrombolysis drug dosage, shorten recanalization time of vessels, thus reducing hemorrhage risk[21]. This study on combined therapy showed lower NIHSS score at 7d and 90d that single application of arterial thrombolysis or mechanical thrombectomy, indicating relatively favorable efficiency for ACI therapy. Notably, in our research, the recanalization rate was 83.33% in combined treatment group, and was significantly higher than single use of arterial thrombolysis or mechanical thrombectomy[22]. Timely recanalization of blocked vessels is crucial for the treatment of ACI, and can largely alleviate the brain tissue damage, improve survival rate and decrease the incidence of complications. On the other hand, combined approaches enable the full exposure of thrombosis lesion to thrombolysis drugs, and thus maximally prevent post-operative hemorrhage, coagulation dysfunction or other complications[23]. In this study, the occurrence of adverse effects in combined group was 16.67%, marginally lower than single usage of arterial thrombolysis or mechanical thrombectomy group although with statistical significance, probably due to relatively smaller sample size in this study.

In recent years, it is still debatable regarding the thrombolytic approaches for ACI, as various methods have both advantages and weakness[24]. This study showed a better clinical efficiency of the treatment of ACI by using mechanical thrombectomy combined with rhPro-UK arterial thrombolysis, additionally without increase of adverse effects. However, the limitation in our study still exists due to relatively smaller samples size. Future studies are required to employ multi-centered research within a large cohort. In clinical practice, it is necessary to deliberately choose optimal thrombolysis approach based on cerebral infarction site, disease onset time and patient conditions, in order to improve survival rate and life quality of patients and diminish prevalence of complication.

Conclusions

We showed that mechanical thrombectomy combined with rhPro-UK arterial thrombolysis treatment has better efficiency in treating moderate to severe ACI than single thrombolysis approach, without significant increase of adverse effects.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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