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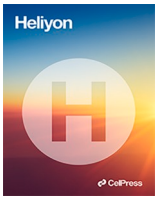

Research article

Combined intravenous and intra-arterial thrombolysis in hyperacute cerebral ischemia without significant corresponding vascular occlusion/stenosis: A Preliminary investigation

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ABSTRACT

Objective: In this study, we assessed the efficacy and safety of various thrombolytic treatment protocols in patients with hyperacute cerebral infarction.

Methods: Patients diagnosed with acute ischemic stroke within 6 h of symptom onset and with brain computer tomography angiography confirming the absence of major vessel stenosis or occlusion were eligible for this study. The enrolled patients were subsequently randomized into two groups: all the groups received the standard intravenous thrombolysis treatment with rt-PA (0.9 mg/kg), and the experimental group underwent sequential intra-arterial thrombolysis treatment with alteplase (0.3 mg/kg, with a maximum dose of 22 mg), administered directly into the target vessel via a microcatheter. Both groups were closely monitored for changes in their National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin scale score, hemorrhage rate, all-cause mortality rate, and the rate of favorable outcomes at 90 ± 7 days.

Results: Ninety-four participants were enrolled in this study, with both the control and experimental groups initiating intravenous injection of rt-PA at a median time of 29 min. For the experimental group, the median time for arterial puncture was 123 min. Baseline data for both groups were similar ($P > 0.05$). Hemorrhagic transformation occurred in 24.47 % (23 patients), with a lower intracranial hemorrhage rate observed in the experimental group compared to the control group (15.2 % vs 33.3 %, $P < 0.05$). Asymptomatic hemorrhage rates were 8.7 % for the experimental group and 12.5 % for the control group, with no hemorrhage detected in other locations. Post-treatment median NIHSS scores were lower in the experimental group than in the control group (7 vs 9, $P < 0.05$), but short-term NIHSS scores were similar ($P > 0.05$). A higher proportion of patients in the experimental group achieved favorable outcomes compared to the control group (87.0 % vs 43.8 %, $P < 0.05$).

Conclusion: In patients with acute ischemic stroke with an onset time of ≤6 h and no major intracranial vessel occlusion, combining rt-PA intravenous thrombolysis with intra-arterial thrombolysis via a microcatheter might yield superior functional outcomes.

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1. Introduction

Acute ischemic stroke is a common neurologic disorder, marked by high incidence, mortality, and disability rates, necessitates swift reperfusion of ischemic brain tissue to salvage vulnerable regions from irreversible damage. Effective reperfusion significantly reduces functional disability and enhances outcomes [1,2].

Venous thrombolysis, the current guideline-recommended approach, promptly recanalizes affected vessels, restoring blood supply to distal areas, and rescuing endangered brain tissue and neurological functions. However, more than 50 % of patients do not recover fully after venous thrombolysis [3,4], and some succumb to the condition. For patients presenting with major vessel occlusion, the prevailing therapeutic approach involves interventional reperfusion. However, a significant challenge arises when patients exhibit high National Institutes of Health Stroke Scale (NIHSS) scores and severe clinical symptoms but do not manifest major vessel occlusion on radiological examinations [5]. These patients often exhibit poor responses due to underlying microcirculation reperfusion issues [6], even when major vessel stenosis or occlusion is absent. Intra-arterial thrombolysis via a microcatheter provides a solution by enabling targeted thrombolytic drug delivery, swiftly enhancing microcirculation, and re-establishing robust blood flow for improved clinical outcomes. Evaluating the benefits and risks associated with endovascular arterial thrombolysis remains a challenge for clinicians, bearing significant implications for clinical decision-making.

In this study, we primarily investigated the effectiveness and safety of sequential venous-arterial thrombolysis treatment in patients with hyperacute cerebral infarction.

2. Materials and methods

General Information: We enrolled 94 patients with acute ischemic stroke admitted to our cerebrovascular disease center between December 2021 to May 2023, meeting the specified inclusion and exclusion criteria. Patients were randomly assigned in a 1:1 ratio using a random number table, resulting in 48 patients in the control group and 46 patients in the experimental group. In the control group, 33 patients were male (68.8 %) and 15 were female (31.2 %) with an average age of 62.79 $\pm$ 9.22 years. In the experimental group, 28 patients were male (60.9 %) and 18 were female (39.1 %) with an average age of 65.17 $\pm$ 13.83 years. All patients provided informed consent, and this research received approval (No.GYLLPJ-20211027-28) from the Medical Ethics Committee of our hospital.

Inclusion Criteria: (1) Definitive diagnosis of acute ischemic stroke with a confirmed onset within $\leq$6 h (2) Age range from 18 to 90 years. (3) NIHSS score of $\geq$8 [5]. (4) Computer tomography angiography revealing no significant stenosis or occlusion in major intracranial vessels. (5) Prior history of cerebral infarction, with a modified Rankin scale (mRS) [7] score of $\leq$2. (6) Computer tomography (CT) scan-based exclusion of intracranial hemorrhage and absence of early signs of extensive cerebral infarction or indirect indications of early infarction. Notably, an old lacunar cerebral infarction may be visible on the CT scan, but without any residual neurological functional deficits. (7) All patients underwent CTP perfusion assessment: rCBF $<$30 %, and the absence of significant abnormal changes in rCBV.

Exclusion Criteria: (1) History of intracranial hemorrhage, including suspected subarachnoid hemorrhage. (2) Recent head trauma within the last 3 months. (3) Gastrointestinal or urinary system bleeding within the past 3 weeks. (4) Major surgical procedures performed within the last 2 weeks. (5) Arterial puncture at a site where hemorrhage control may be challenging within the past week. (6) History of cerebral infarction or myocardial infarction within the past 3 months. (7) History of cerebral infarction but no symptoms of neurological deficit (mRS = 0). (8) Evidence of active bleeding or trauma on physical examination (9) Severe cardiac, liver, kidney dysfunction, or a significant history of diabetes mellitus. (10) Platelet count $<100 \times 10^9$/L, blood glucose $<$2.7 mmol/L; systolic blood pressure $>$180 mmHg or diastolic $>$100 mmHg. (11) Oral intake of anticoagulant drugs with INR (International Normalized Ratio) $>$ 1.5 or recent heparin therapy within the last 48 h (12) Non-compliant patients. (13) Patients who experienced epileptic seizures at onset.

2.1. Treatment method

Patients in the control group received a standard dosage of venous thrombolysis with alteplase, totaling 0.9 mg/kg or a maximum of 90 mg. Of this dose, 10 % was administered intravenously within 1 min, while the remainder was diluted in saline and infused over 1 h using a micro-pump. Following thrombolysis completion, standard antiplatelet medications were initiated 24 h later. This regimen included aspirin enteric-coated tablet (100 mg/d) and clopidogrel tablet (75 mg/d), supplemented with atorvastatin calcium tablet for anti-arteriosclerosis treatment. After administering the standard dose of rt-PA (recombinant tissue plasminogen activator) venous thrombolysis, the patients were promptly transferred to the neurointerventional suite. The procedure involved a femoral arterial puncture approach to insert a 6F arterial sheath. A 6F guiding catheter was advanced into the symptomatic artery under guidewire guidance. Subsequently, a microcatheter was guided to the target vessel (anterior cerebral artery A2 segment, middle cerebral artery M1 terminal, or vertebrobasilar artery origin) under micro guidewires. In cases where vessel tortuosity posed safety concerns, the microcatheter was positioned as high as possible in the internal carotid artery or vertebral artery. After removing the micro guidewire, rt-PA equivalent to one-third of the venous thrombolysis dose (0.3 mg/kg, maximum 22 mg) dissolved in 20 ml of saline [8,9], was slowly infused through the microcatheter over 20 min. Throughout the thrombolysis process, patients' vital signs including respiratory rate, blood pressure, heart rate, rhythm, pupil size, consciousness, speech, and limb movements were continuously monitored. Immediately post-procedure, a dynamic CT (Dyna CT) was conducted to assess for any signs of bleeding. At 24 h post-thrombolysis, patients were administered aspirin enteric-coated tablet (100 mg/d) and clopidogrel tablet (75 mg/d). The determination of the target vessel was made by two or more associate chief physicians in neurology based on the patient's clinical symptoms. Thrombolysis via

RT-PA was terminated if any of the following occurred: (1) Unexplained early signs of cerebral edema. (2) Suspected contrast agent leakage indicating possible vessel rupture. (3) Dyna-CT before rt-PA administration reveals bleeding (if the patient's condition worsens and Dyna-CT does not show signs of bleeding, the procedure was restarted). (4) Clinical symptoms worsen and this worsening cannot be explained by the angiography results. (5) Onset of epileptic seizures during the treatment process. (6) Concurrent myocardial infarction. In addition to these established criteria for ceasing intra-arterial injection of rt-PA, researchers relied on their clinical experience to assess the risks and benefits of treatment for each patient and make informed decisions regarding the timing of rt-PA cessation.

2.2. Observational indicators

(1) At 24 h (±6 h) post-treatment, a non-contrast computer tomography (NCCT) scan was performed to detect intracranial hemorrhage, encompassing both symptomatic and asymptomatic cases [10,11]. Patients underwent assessments immediately post-treatment, at 24 ± 6 h, 7 ± 2 days, and 90 ± 7 days, which encompassed: NIHSS score [5], mRS score [7], hemorrhage rate, and complication rate. Patient prognosis was further evaluated using the mRS assessment at 90 ± 7 days.

Definition: mRS was employed to evaluate post-stroke disabilities and functional status [7]. The mRS score categories are as follows: 0: No symptoms; 1: Minor symptoms, no significant disabilities, normal daily activities unaffected; 2: Mildly disabled, unable to perform all previous activities but can manage daily affairs; 3: Moderate disability, requires assistance with daily activities but can walk unassisted; 4: Moderately severe disability, requires assistance to walk and cannot manage daily affairs; 5: Severe disability, bedridden, incontinent; 6: Deceased.

An mRS score of $\leq$2, signifying functional independence, suggests a favorable prognosis, while a score of $\geq$3 indicates an unfavorable prognosis.

(2) Primary safety indicators: Life-threatening hemorrhagic complications [10,11] occurring within 24 ± 12 h after RT-PA infusion. These complications encompass: 1) Development of intracerebral hematoma or hemorrhagic infarction leading to permanent disability or fatality. 2) Other severe systemic hemorrhagic complications, such as groin hematoma, retroperitoneal hematoma, or gastrointestinal bleeding, necessitating blood transfusion or major surgical intervention. 3) Intracranial hemorrhage is classified into symptomatic intracranial hemorrhage and asymptomatic intracranial hemorrhage, as defined in the ECASS trial [10,11].

Secondary safety indicators: Comparison of the incidence of intracranial hemorrhage post treatment between the two patient groups. Assessment of the bleeding incidence at other sites, encompassing skin and mucosal bleeding, gastrointestinal bleeding, and gum bleeding. Evaluation of the overall mortality rate.

During the follow-up period, evaluation of NIHSS score and mRS evaluations were carried out by impartial researchers who were not involved in the patient's treatment and were unaware of treatment assignments [5,7]. The patient's pre-stroke functional status was assessed using previously documented mRS scores from their medical history [7].

2.3. Statistical analysis

In this study, a generalize linear model was used to analyze the difference in the proportion of modified Rankin scale (mRS) 0–2 at 90 (±7) days between the two groups. The primary efficacy endpoint was the proportion of patients with an mRS Score of 0–2 at 90 (±7) days post-enrollment (binary categorical variable). According to previous meta analysis and IMS-II analysis reports, the parameters were set as follows: (1) The proportion of patients with mRS Score 0–2 at 90 days (±7 days) in the control group was 38 %; (2) The proportion of patients with mRS Score 0–2 at 90 days (±7 days) in the experimental group was 60 %; (3) Calibration test level $\alpha = 0.05$ (bilateral), $1\text{-}\beta = 0.80$; (4) The sample size of the experimental group and the control group was allocated in a 1:1 ratio. Considering the 20 % shedding rate, the final total sample was set at 94 cases, with 47 cases in each group.

Data processing was performed using SPSS 19.0 statistical software. Quantitative data following a normal distribution are expressed as mean ± standard deviation ($\overline{x} \pm s$), and group comparisons were conducted using a one-way ANOVA or independent samples *t*-test. Non-normally distributed quantitative data are described using median and interquartile ranges, with group comparisons using a rank-sum test. Categorical data are expressed as percentages, and group comparisons were carried out using a chi-squared (χ^2) test. In cases where the theoretical frequency was <5, a continuity-adjusted χ^2 test was applied. A significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline data and clinical Characteristics

(1) **Control Group:** Within the control group, 33 individuals were male (68.8 %) and 15 were female (31.2 %). The average age was 62.79 ± 9.22 years, with a median time from symptom onset to hospital arrival of 240 min. Among them, 26 cases (54.2 %) had hypertension, and 5 cases (10.4 %) had diabetes.

Experimental Group: In the experimental group, there were 28 males (60.9 %) and 18 females (39.1 %). The average age was 65.17 ± 13.83 years, with a median time from symptom onset to hospital arrival of 240 min. Among them, 20 cases (43.5 %) had hypertension, and 3 cases (6.5 %) had diabetes mellitus.

(2) Both groups presented with a median emergency NIHSS score of 12, a median mRS score of 4 upon admission, and a median Door to Needle Time (DNT) of 29 min. The experimental group had a median Door to Arterial Puncture Time (DPT) of 123 min. Comparison of baseline data between the two groups revealed no statistical significance ($P > 0.05$), ensuring their comparability. For details, refer to Table 1.

3.1.1. Comparison of NIHSS and mRS scores 24 ± 6h after treatment and at 7 ± 2d between the two groups

(1) Immediately post-treatment, the control group exhibited a median NIHSS score of 9, whereas the experimental group had a median score of 7. The P value was 0.035, which is less than 0.05, indicating statistical significance. This suggests that the combination of venous thrombolysis with intra-arterial thrombolysis can improve microcirculation, enhance reperfusion, and lead to quicker improvement in neurological function symptoms.
(2) After 24 ± 6 h of treatment, 23 patients (47.9 %) in the control group experienced a reduction in NIHSS score of ≥4 points, compared to 27 (58.7 %) in the experimental group. Conversely, early neurological deterioration, marked by an increase in the NIHSS score of >4 points, was observed in 9 patients (18.8 %) from the control group and 4 patients (8.7 %) from the experimental group. This suggests that after early thrombolysis, there is a potential recurrence of microemboli dissolution leading to neurological function disorders. The experimental group had fewer cases of deterioration than the control group, although there was no statistical difference between the two groups.

Table 1
Baseline Patient data.

Characteristics		Control group (n = 48)	Experimental group (n = 46)	P-value
Male (%)		33 (68.8)	28 (60.9)	0.00
Female (%)		15 (31.2)	18 (39.1)	
Age		62.79 ± 9.22	65.17 ± 13.83	0.331
mRS score before onset (IQR)		0 (0,2)	0 (0,2)	0.522
Time from onset to hospital arrival, min (IQR)		240 (179,318)	240 (172,300)	0.364
Emergency NIHSS score (National Institutes of Health Stroke Scale) (IQR)		12 (9,14)	12 (9,15)	0.666
mRS score upon admission (IQR)		4 (4,4)	4 (4,4)	0.627
History of atrial fibrillation (%)		0 (0)	1 (2.2)	0.304
History of hypertension (%)		26 (54.2)	20 (43.5)	0.300
History of diabetes mellitus (%)		5 (10.4)	3 (6.5)	0.499
History of stroke (%)		15 (31.3)	13 (28.3)	0.751
History of coronary artery disease (%)		3 (6.3)	4 (8.7)	0.652
Blood glucose level upon admission, mmol/l		7.4 ± 3.06	7.89 ± 3.09	0.434
LDL (low-density lipoprotein) level upon admission, mmol/l		3.19 ± 0.99)	3.50 ± 1.51	0.230
Cholesterol level upon admission		4.64 ± 1.14	5.11 ± 1.86	0.143
Homocysteine level upon admission		13.58 ± 6.05	15.24 ± 6.74	0.214
The lesion of cerebral infarction	Basal ganglia	17 (35.4)	17 (37.0)	0.367
	Corona radiata	10 (20.8)	5 (10.9)	
	Brain stem	7 (14.6)	7 (15.2)	
	Lobus parietalis	6 (12.5)	10 (21.7)	
	Occipital lobe	4 (8.3)	4 (8.7)	
	Thalamus	3 (6.3)	0 (0)	
	Frontal lobe	0 (0)	2 (4.3)	
	Cerebellar hemispheres	1 (2.1)	1 (2.2)	
DNT time, min (IQR)		29 (27,30)	30 (25,38)	0.059
DPT time, min (IQR)			123 (105,149)	

Note: Please note that ± values represent ± standard deviation (SD). In cases where no significant difference exists between the two groups, percentages may not sum to 100 due to rounding. The interquartile range (IQR) is also used to denote variability.
The NIHSS serves as a standardized neurological examination, with scores ranging from 0 (representing normal function) to 42 (indicating a fatal condition). Lower scores correspond to milder strokes. mRS is employed to assess post-stroke disability and functional status, with scores categorized as follows.
0: No symptoms.
1: Minor symptoms, no significant disabilities, unaffected daily activities.
2: Mildly disabled, unable to carry out all previous activities but can manage daily affairs.
3: Moderate disability, requires help with daily activities but can walk unassisted.
4: Moderately severe disability, requires assistance to walk and cannot manage daily affairs.
5: Severe disability, bedridden, incontinent.
6: Deceased.

At 7 ± 2 days, the median NIHSS and mRS scores were 7 for the control group and 5 for the experimental group. However, there was no significant statistical difference between the two groups. See Table 2.

3.1.2. Comparison of complications and intracranial hemorrhage rate after thrombolytic treatment between the two groups

In the control group, out of 29 cases, 23 (24.47 %) patients exhibited hemorrhagic transformation, with 10 (10.64 %) of them being asymptomatic. In contrast, the experimental group had 16 (33.3 %) patients with hemorrhagic transformation, including 6 (12.5 %) who were asymptomatic. In the experimental group, 7 (15.2 %) experienced hemorrhagic transformation with 4 (8.7 %) being asymptomatic hemorrhages. No hemorrhage incidents were reported in other regions. The P value was 0.019, indicating a statistically significant difference between the two groups. Please refer to Table 3.

3.1.3. Comparison of 90 ± 7d mRS scores and prognosis between the two groups

At 90 ± 7 days, 21 patients (43.8 %) from the control group exhibited a favorable outcome, whereas 40 patients (87.0 %) in the experimental group had a favorable outcome. The difference between the groups was statistically significant ($P < 0.05$). This indicates that the sequential venous-arterial thrombolysis treatment yields a superior overall efficacy rate for the prognosis of acute ischemic stroke in the experimental group compared to the control group ($P < 0.05$). Please refer to Table 4 and Fig. 1.

4. Discussion

Cerebral infarction is a prevalent condition among the elderly and is among the top three causes of human mortality today. It poses a significant threat to individuals and society as a whole. Venous thrombolysis is currently regarded as the most effective treatment for ischemic stroke [1], as it can significantly reduce the incidence of functional disability [1]. Venous thrombolysis treatment offers several advantages, including prompt initiation following clinical and imaging assessments. Additionally, it utilizes straightforward technical equipment, is cost-effective, and is well-accepted by patients. Venous thrombolysis aids in rescuing endangered brain tissue and facilitates the restoration of normal neural function. However, studies suggest that over 50 % of patients with acute ischemic stroke do not achieve effective recovery following venous thrombolysis [3,4], with some even succumbing to the condition. These patients are believed to have a microcirculation reperfusion disorder [6], possibly due to the formation of microemboli or microemboli resulting from clot dissolution post venous thrombolysis. These microemboli can obstruct peripheral microcirculation reperfusion, a challenge not addressed by interventional reperfusion methods. On the contrary, local intra-arterial thrombolysis presents advantages over venous thrombolysis [12]. It allows for the assessment of the compensatory degree and blood flow reperfusion at the distal end of the responsible blood vessel using digital subtraction angiography (DSA). By selectively and precisely administering thrombolytic agents at high concentrations within the target blood vessel, it can expedite microcirculation improvement. Results from the IMS stroke intervention trial [13,14] suggest that sequential venous-arterial thrombolysis can yield better clinical outcomes.

In this study, the median NIHSS score immediately after rt-PA venous thrombolysis treatment in the control group was 9. In contrast, the experimental group, which underwent combined intravenous and intra-arterial thrombolysis, had a median NIHSS score of 7. This statistical divergence implies that the combination of venous and intra-arterial thrombolysis swiftly enhances microcirculation, promotes reperfusion, and expeditiously alleviates neurological symptoms, achieving early arterial complete reperfusion. There were 23 cases (47.9 %) with an NIHSS score reduction of ≥4 points at 24 ± 6 h post-treatment, compared to 27 cases (58.7 %) in the experimental group. Meanwhile, early neurological deterioration, marked by an increase in the NIHSS score of >4 points, was observed in 9 patients (18.8 %) in the control group and 4 patients (8.7 %) in the experimental group. This decline in condition may be attributed to the resurgence of distal microemboli fusion following thrombolysis, causing microcirculation obstruction and subsequent neurological dysfunction [15]. Notably, the experimental group appeared more susceptible to microemboli dissolution. At 7 ± 2d, median NIHSS and mRS scores were 7 for the control group and 5 for the experimental group. While the experimental group experienced fewer deteriorations, statistical significance was not achieved, possibly due to the study's limited sample size.

At 90 ± 7 days, the comparison of neurological prognosis revealed that 21 patients (43.8 %) in the control group exhibited a favorable prognosis, while a substantial 40 patients (87.0 %) in the experimental group demonstrated the same. The statistical significance ($P < 0.05$) underscores the superior neurological outcomes attained through sequential venous-arterial thrombolysis treatment. It echoes findings from the meta-analysis conducted by Ma et al. [16], which also emphasized significantly better outcomes with intra-arterial thrombolysis compared to venous thrombolysis. The combination of venous thrombolysis with intra-arterial thrombolysis capitalizes on the strength of both approaches. It achieves optimal treatment timing by administering venous

Table 2
Comparison of early clinical neurological function impairment between the two groups.

	Control group (n = 48)	Experimental group (n = 46)	Z value	P-value
NIHSS score immediately after treatment (IQR)	9 (7,13)	7 (4,12)	−2.114	0.035
NIHSS score 24 ± 6 h post-treatment (IQR)	7 (3,11)	7 (4,11)	−0.868	0.385
≥4-point reduction in NIHSS score 24 ± 6 h post-treatment (%)	24 (50)	27 (58.7)	0.716	0.398
4-point increase in NIHSS score 24 ± 6 h post-treatment (%)	9 (18.8)	4 (8.7)	1.993	0.158
NIHSS score 7 ± 2 days post-treatment	7 (1,12)	5 (3,11)	−0.637	0.527
mRS score 7 ± 2 days post-treatment	3 (1,4)	3 (2,4)	−0.395	0.693

Note: The NIHSS is a standardized neurological examination, with scores ranging from 0 (indicating normal function) to 42 (indicating death). A lower score indicates a milder stroke. mRS refers to the Modified Rankin Scale.

Table 3
Comparison of hemorrhage rate between the two groups post thrombolytic treatment.

	Control group (n = 48)	Experimental group (n = 46)	χ2	P-value
Complications (%):				0.019
None	29 (60.4)	39 (84.8)	7.95	
Yes	19 (39.6)	7 (15.2)		
Infarct expansion (%)	3 (6.3)	0 (0)		
Hemorrhagic transformation (%)	16 (33.3)	7 (15.2)	5.46	0.020
Symptomatic intracranial hemorrhage (%)	10 (20.8)	3 (6.5)		
Asymptomatic intracranial hemorrhage (%)	6 (12.5)	4 (8.7)		
Gastrointestinal bleeding (%)	0 (0)	0 (0)		
Cutaneous and mucosal bleeding (%)	0 (0)	0 (0)		

Table 4
Comparison of good prognosis rate between the two groups at 90 ± 7 days.

	Control group (n = 48)	Experimental group (n = 46)	χ2	P-value
90 ± 7 days mRS, (Median)	3 (0,3)	0 (0,2)	−3.211	0.001
Good prognosis (%)	21 (43.8)	40 (87.0)	19.25	0.00
Poor prognosis (%)	27 (56.3)	6 (13.0)		
Death (%)	0 (0)	0 (0)		

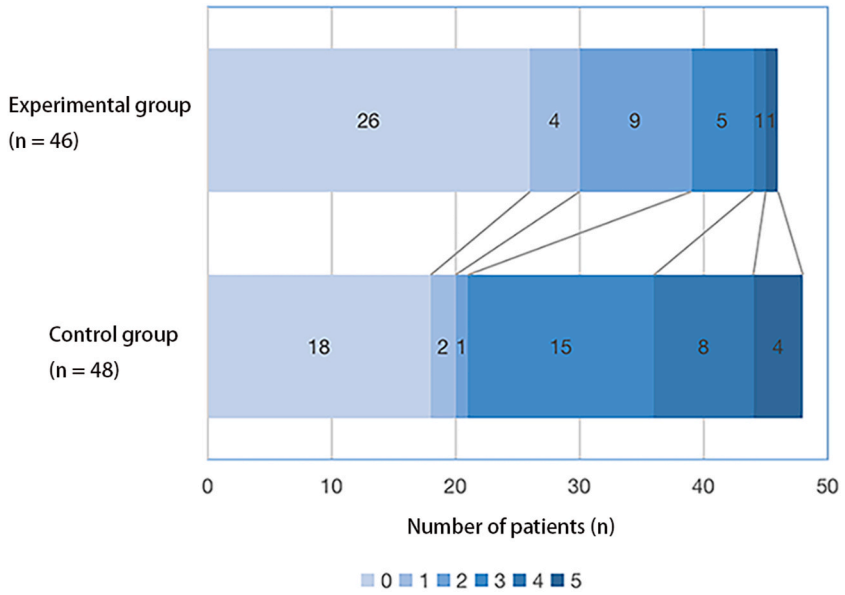

Fig. 1. 90 ± 7 days mRS score.

thrombolysis drugs promptly and concentrates them at the thrombus site, maximizing microcirculatory improvements for an ideal thrombolytic effect. However, broader randomized prospective studies are warranted to validate this conclusion.

In the earliest study on intra-arterial thrombolysis [17], the intracranial hemorrhage rate within 24 h for intra-arterial thrombolysis stood at 42 %, accompanied by a 27 % mortality rate. Subsequent investigations have reported mortality rate for intra-arterial methods spanning from 7 % to 29 % [18]. In our current study, a total of 23 patients (24.47 %) experienced hemorrhagic transformation, including 10 cases (10.64 %) with asymptomatic hemorrhage. Within the control group, 16 cases (33.3 %) of hemorrhagic transformation were observed, with 6 cases (12.5 %) being asymptomatic. In contrast, the experimental group had 7 case (15.2 %) of hemorrhagic transformation, with 4 cases (8.7 %) being asymptomatic. Notably, the P-value of 0.019 and no recorded deaths highlights a statistically significant difference between the two groups. The bleeding rate of the experimental group after receiving higher dose of rt-PA is lower than that of the control group. The possible reasons are as follows: 1.the small sample size; 2. There are many causes of intracranial hemorrhage, including: (1) vascular wall injury after ischemia; (2) the function of blood-brain barrier was destroyed in the late infarction, which increased the permeability and caused reperfusion bleeding; (3) the amount of thrombolytic drugs is too large. However, the bleeding rate of the experimental group is low, considering that arterial thrombolysis can obtain a higher concentration of thrombolysis at the target, which can quickly restore cerebral blood perfusion, improve the phenomenon of

non-reflow caused by microcirculation disorders, reduce the destruction of the blood-brain barrier caused by brain cell ischemia and hypoxia, achieve early complete arterial recirculation in a real sense, and improve neurological function symptoms, therefore reducing the risk of intracranial. In addition, this finding underscores that the integration of venous thrombolysis with intra-arterial thrombolysis does not increase the risk of intracranial hemorrhage and is associated with fewer adverse reactions, underscoring its enhanced safety profile.

5. Limitation

In this study, the patients enrolled were recruited in one center with small sample size. Moreover, we found there were some patients with high NIHSS score and severe neurological dysfunction symptoms at the onset, but no large vessel occlusion was found in intracranial imaging examination, and the therapeutic effect of intravenous thrombolysis in these patients was not satisfactory. Therefore, a large sample size form multiple centers were necessary in the future.

6. Conclusion

In this study, the combination of venous thrombolysis and arterial intervention through intra-arterial thrombolysis treatment yields a notably higher rate of favorable prognosis without elevating the risk of intracranial hemorrhage. It might help clinicians to choose a better treatment in patients with hyperacute cerebral infarction.

Data availability statement

Data included in article/supp. material/referenced in article. The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of our hospital (No.GYLLPJ-20211027-28). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

CRediT authorship contribution statement

Xinming Li: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Yan Tan:** Writing – original draft, Data curation. **Jinzhao Song:** Writing – original draft, Data curation. **Hongying Lu:** Writing – original draft, Data curation. **Yuan Bian:** Writing – original draft, Data curation. **Wenqiang Cai:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

CTA	CT angiography
rt-PA	recombinant tissue plasminogen activator
NIHSS	National Institute of Health stroke scale
mRS	Modified Rankin Scale
CTP	computer tomography perfusion imaging
rCBF	region cerbral blood flow
rCBV	region cerebral blood volume
DNT	Door -To-Needle Time
DPT	Door-To-Puncture time

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