

# Intra-Arterial vs Intra-Venous Thrombolysis for Anterior Cerebral Occlusion

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**ABSTRACT: Background:** The safety and effectiveness of intra-arterial thrombolysis (IAT) in comparison to intravenous thrombolysis (IVT) for the treatment of ischemic stroke is uncertain. Our study aims to assess and compare IAT to IVT for clinically relevant outcomes in patients with occlusion of the anterior cerebral circulation. **Methods:** Patients with acute ischemic stroke were enrolled for either treatment; those whose symptoms occurred within 4.5 hrs after stroke were treated with IVT, whereas those who presented <4.5 hrs but had contraindications to IVT or presented between 4.5 and 6 hrs were treated with IAT. Evaluated endpoints included: disability at 90 days as measured by the modified Rankin Scale (mRS), incidence of mortality, and incidence of symptomatic intracranial haemorrhage. **Results:** 78 patients with anterior cerebral circulation occlusion were included in the study (55 in IVT, 23 in IAT). After 90 days, 82.6% patients treated with IAT reached independence in comparison to 56.4% in the IVT group ( $P=0.028$ ,  $RR=2.66$ , 95% CI: 1.10-7.04). The incidence of all intracranial haemorrhages in the IAT and IVT groups respectively were 30.4% and 12.7% ( $P=0.103$ ,  $RR=2.391$ , 95% CI: 0.946-6.047); symptomatic intracranial haemorrhage occurred in 8.7% and 9.1% of patients ( $P=1.00$ ,  $RR=0.957$ , 95% CI: 0.200-4.579), and mortality in 8.7% and 16.4% ( $P=0.492$ ,  $RR=1.882$ , 95% CI: 0.440-8.045). **Conclusion:** Results suggest that IAT is more effective than IVT in allowing patients to achieve independence. While inconclusive, the safety of IAT within 6 hrs is comparable to IVT within 4.5 hrs.

**RÉSUMÉ: Thrombolyse intra-artérielle versus intraveineuse pour traiter l'occlusion de l'artère cérébrale antérieure. Contexte :** La sécurité et l'efficacité de la thrombolyse intra-artérielle (TIA) comparée à la thrombolyse intraveineuse (TIV) dans le traitement de l'accident vasculaire cérébral (AVC) sont mal connues. Le but de cette étude était d'évaluer et de comparer la TIA et la TIV quant aux résultats cliniques pertinents chez les patients atteints d'une occlusion de la circulation cérébrale antérieure. **Méthodes :** Des patients atteints d'un AVC ischémique aigu ont été inclus dans cette étude. Ceux dont les symptômes duraient depuis 4,5 heures ou moins étaient traités par TIV alors que ceux dont les symptômes duraient depuis moins de 4,5 heures mais qui avaient des contre-indications à la TIV ou qui se présentaient entre 4,5 et 6 heures ont reçu une TIA. Les résultats évalués étaient les suivants: l'invalidité après 90 jours selon l'échelle de Rankin modifiée, l'incidence de mortalité et l'incidence d'hémorragie intracrânienne symptomatique. **Résultats :** Soixante-dix-huit patients atteints d'occlusion de la circulation cérébrale antérieure ont été inclus dans l'étude, soit 55 dans le groupe TIV et 23 dans le groupe TIA. Après 90 jours, 82,6% des patients traités par TIA étaient redevenus indépendants par rapport à 56,4% des patients traités par TIV ( $p = 0,028$ ;  $RR = 2,66$ ; IC à 95% de 1,10 à 7,04). L'incidence d'hémorragie intracrânienne dans les groupes TIA et TIV étaient de 30,4% et 12,7% respectivement ( $p = 0,103$ ;  $RR = 2,391$ ; IC à 95% de 0,946 à 6,047); 8,7% et 9,1% des patients respectivement ont présenté une hémorragie intracrânienne symptomatique ( $p = 1,00$ ;  $RR = 0,957$ ; IC à 95% de 0,200 à 4,579) et 8,7% et 16,4% des patients respectivement sont décédés ( $p = 0,492$ ;  $RR = 1,882$ ; IC à 95% de 0,440 à 8,045). **Conclusion :** Selon nos résultats, un plus grand nombre de patients recouvrent leur autonomie lorsqu'ils sont traités par la TIA plutôt que par la TIV. Bien que cette étude ne permette pas de l'affirmer avec certitude, il semble que la sécurité de la TIA en dedans de 6 heures soit comparable à celle de la TIV en dedans de 4,5 heures.

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The National Institute of Neurological Disorders and Stroke (NINDS) study demonstrated a beneficial effect of intravenous tissue plasminogen activator (rt-PA) when given within three hours after symptom onset<sup>1</sup>. In the pooled analysis, thrombolysis was approved and recommended as a first-line treatment for acute ischemic stroke patients within three hours after the onset of stroke<sup>2-6</sup>. However, fewer than 2% of patients receive intravenous alteplase within three hours in most countries, primarily because of delayed admission to a stroke centre<sup>7</sup>. The recent European Cooperative Acute Stroke Study III (ECASS III)<sup>7</sup> and Safe Implementation of Thrombolysis in Stroke-

International Stroke Thrombolysis Register (SITS-ISTR)<sup>8</sup> studies found that intravenous alteplase administered between 3

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and 4.5 hours after onset of stroke symptoms was safe and effective in patients with acute ischemic stroke<sup>7,8</sup>. Intra-arterial thrombolytic therapy for acute ischemic stroke might be a treatment option with an expanded treat-time window, and it could be beneficial to patients less likely to respond to or in whom it is not desirable to intravenous thrombolysis<sup>9</sup>. Some studies<sup>10-13</sup> compared the efficacy of intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT), with results showing a higher recanalization rate in occlusions of the middle cerebral artery and basal arterial from IAT as opposed to IVT. Intravenous thrombolysis was also associated with significantly improved clinical outcomes. The data currently available is inadequate for making clear treatment decisions regarding thrombolytic treatments for ischemic stroke<sup>14</sup>. Various protocols and heterogeneous evaluated endpoints used in the studies do not allow for good comparisons. This study aims to compare the effectiveness and safety of IAT provided within six hours to IVT provided within a 4.5 hour time window for patients with anterior cerebral circulation occlusion.

## MATERIALS AND METHODS

The patients were recruited from 2003 to 2008 at Shanghai Sixth People's Hospital affiliated to Shanghai Jiaotong University, China. The inclusion and exclusion criteria were same as the NINDS study<sup>1</sup>. For inclusion: patients had to be between 18 and 80-years-old and have a base-line brain computed tomographic (CT) scan indicating no evidence of intracranial haemorrhage. In addition, patients had to have a National Institutes of Health Stroke Scale (NIHSS) score between 4 and 24 and not have experienced another stroke or serious head trauma within the preceding three months or have had major surgery within 14 days. Patients were excluded if they were comatose, had a history of intracranial hemorrhage, potential subarachnoid haemorrhage, gastrointestinal haemorrhage or urinary tract haemorrhage within the previous 21 days. Patients with a systolic blood pressure above 185 mm Hg or diastolic blood pressure above 115 mm Hg were excluded as were people with an arterial puncture at a noncompressible site

in the previous seven days. Patients experiencing a seizure at the onset of stroke; taking anticoagulants or heparin within the 48 hours preceding the onset of stroke, and those with an elevated partial-thromboplastin time (including prothrombin times greater than 15 seconds, platelet counts below 100,000/mm<sup>3</sup>, or glucose concentrations below 2.7 mmol/L per or above 24 mmol/L) were also excluded from enrollment.

The ethics committee of the Shanghai Sixth People's Hospital affiliated to Shanghai Jiaotong University approved this study protocol. All patients or legally authorized representatives provided written informed consent before thrombolysis.

Patients who presented within 4.5 hours from symptom onset were treated by intravenous thrombolysis with alteplase (Actilyse, Boehringer Ingelheim) at a dosage of 0.9 mg/kg body weight (maximum 90 mg)<sup>1</sup>. Those who presented within 4.5 hrs but had contraindications to IVT (i.e. severe neurological deficits (NIHSS score > 20), recent history of major surgical procedures, embolic stroke or occlusion of major cervical and/or intracranial vessels), or presented at an interval between 4.5 and 6 hours after onset were treated with intra-arterial thrombolysis (IAT). In the IAT group, patients underwent MRI (include the Diffusion-weighted of magnetic resonance imaging (DWI) and Perfusion-weighted of magnetic resonance imaging (PWI) to identify the ischemic penumbra), MRA to identify infarction location and digital subtraction angiography (DSA) to identify occlusive site and lateral branch circulation. Patients with arterial occlusion on DSA underwent IAT. Micro-catheter was inserted into affected segments or the clots directly, and then thrombosis medication (rt-PA 1ml/min, max: 30mg) was infused. Mechanical disruption using a guide wire was provided when rt-PA administration was not effective. However, it could not be used for recanalization independently. At the end of IAT, DSA was repeated with the indwelling catheter to assess the effect of the intervention and the degree of recanalization. Patients were heparinised during the whole procedure.

During the thrombolytic procedures, blood pressure and blood glucose were monitored every 15 minutes, and kept lower than 185/110 and 24mmol/L respectively through the use of

**Table 1: Baseline characteristics of the patients**

Treatment	IAT	IVT	P Value
Patients, n	23	55	
Mean age ± SD (y)	61.7±11.6	66.6±9.3	0.083
Mean time ± SD (h)	4.6±1.3	3.1±0.5	0.000 *
Men, n (%)	18 (78.3)	41(74.5)	0.727
NIHSS score median (range)	9 (4-24)	9 (4-20)	0.253
Systolic blood pressure ±SD (mmHg)	143.7±28.5	155.6±23.4	0.097
Diastolic blood pressure±SD (mmHg)	84.7±15.5	89.8±13.4	0.093
Blood glucose ±SD (mmol/l)	7.1±3.5	7.4±4.1	0.704
Hypertension, n (%)	15 (65.2)	32(58.2)	0.563
Diabetes mellitus, n (%)	3(13.0)	9 (16.4)	1.000
Atrial fibrillation, n (%)	8 (34.8)	19 (34.5)	0.984

P indicates the difference between groups. \*  $P < 0.05$ .

Labetalol 10-20mg and insulin when necessary.

A follow-up CT scan was obtained approximately 24 hours post-thrombolysis to exclude haemorrhages in both IVT and IAT groups; MRA was conducted to assess perfusion of occluded vessels only in the IAT patients. All patients were treated with low-molecular-weight heparins (5000 U/d subcutaneously administered) for 14 days and then enteric coated aspirin tablets 100-mg/d given for secondary prevention. Blood pressure was to be kept between 180/100-105 mm Hg for those with a history of hypertension and 160-180/90-100 mm Hg for those without a history of hypertension. The anti-hypertensive drugs Labetalol or Sodium Nitroprusside were prescribed if necessary.

The endpoints evaluated for all participants included the NIHSS, a designation of independence, mortality, intracranial hemorrhage, and other complications. National Institutes of Health stroke scale scores were taken at the time of enrolment (baseline), at 24 hours, and 14 days after the treatment. Neurological improvement was defined as an improvement in the 24 hour NIHSS score by four points over baseline or resolution of neurological deficit within 24 hour<sup>15</sup>. Independence at Day 90 was assessed by the modified Rankin scale (mRS), dichotomized as independence (score from 0 to 2) or dependence (score from 3 to 6). Overall mortality was assessed at Day 90 as well evidence of intracranial hemorrhage including symptomatic intracranial hemorrhage (sICH). Symptomatic intracranial hemorrhage was defined as any apparent extravascular blood in the brain or within the cranium associated with clinical deterioration. Deterioration was defined by an increase of four or more points in the score on the NIHSS, or if it led to death. Intracranial hemorrhage has been identified as the predominant cause of post stroke neurologic deterioration<sup>3,7</sup>. In addition, complications such as pneumonia septicemia, and deep venous thrombosis were monitored during hospitalization.

Recanalization was classified according to “thrombolysis in myocardial infarction” (TIMI). Recanalization and perfusion of occluded vessels was categorised as TIMI-0: absent recanalization, TIMI-1: minimal recanalization, TIMI-2: partial recanalization and TIMI-3: complete recanalization.

The same unblinded treatment physician (Sun X) assessed NIHSS scores and mRS scores in all patients during hospitalization. After 90 days follow-up 52 patients were assessed by telephone interview and 26 patients were assessed by an interview with their proxy. The interviewer was unblinded to the patients' treatment.

#### Data Analysis

The difference in incidence of symptomatic intracerebral haemorrhage, mortality, and independence between groups were calculated with the chi-square test. We report on the Relative Risk [RR] and appropriate 95% Confidence Intervals [CIs] for outcomes according to the number of events. National Institutes of Health stroke scale, an ordered categorical scale was presented with median and full range with the Mann-Whitney U test used to test differences between the groups. In the continuous data, this is presented as a mean (with SD). We used the unpaired t test to calculate the difference between the groups. All tests were conducted with the SPSS 11.0 statistical package. P-values are 2-sided with a p-value <0.05 considered significant. ZB conducted the analysis.

#### RESULTS

Between Mar 2003 and Oct 2008, 124 patients fit the thrombolysis criteria, and 83 patients accepted treatments of which 78 had occlusion in the anterior cerebral circulation and were enrolled (23 for IAT and 55 for IVT). No patients were lost to

**Table 2: The outcome of intravenous thrombolysis and intra-arterial thrombolysis**

Treatment (total number)	IVT (55)	IAT (23)	P
NIHSS improvement by $\geq 4$ or decreased to 0 at 24 hours, n (%)	14 (25.5)	10 (43.5)	0.116
24h NIHSS median (range)	7 (0-20)	7 (0-34)	0.660
14d NIHSS median (range)	4 (0-15)	5 (0-20)	0.711
Incranial haemorrhage, n (%)	7 (12.7)	7 (30.4)	0.103
symptomatic intracranial haemorrhaging, n (%)	5 (9.1)	2 (8.7)	1.000
Independence at 3 months, n (%)	31 (56.4)	19 (82.6)	0.028 *
Death within 3 months, n (%)	9 (6.4)	2 (8.7)	0.492

P indicates the difference between groups. \*  $P < 0.05$ .

follow-up. Mean time between presentation and treatment was longer in the IAT (4.6±1.3 hours) group than in the IVT group (3.1±0.5 hours;  $P=0.000$ ), there was no significant difference in age, blood pressure, blood glucose, and NIHSS baseline score between the groups (see Table 1).

Twenty-four hour post-thrombotic NIHSS score was 7 (0-20) and 7 (0-34) in the IAT and IVT groups respectively ( $P=0.660$ ). On the 14th day, NIHSS score was 4 (0-15) and 5 (0-20) in IAT and IVT groups ( $P=0.711$ ) (See Table 1). In the IAT group, 10 patients (43.5%) experienced improvement by  $\geq 4$  points or a decrease to 0 points on the NIHSS at 24 hours after stroke onset, compared with 14 patients (25.5%) in the IVT groups ( $P=0.116$ ,  $RR=1.708$ ; 95% CI: 0.892-3.270). Three months follow-up, mRS scores demonstrated that 19 of 23 (82.6%) patients in the IAT group reached independence compared with 31 of 55 (56.4%) patients in the IVT group ( $P=0.028$ ,  $RR=2.66$ ; 95% CI: 1.10-7.04). The incidence of intracranial haemorrhage in IAT and IVT group was 30.4% and 12.7% respectively ( $P=0.103$ ,  $RR=2.391$ ; 95% CI: 0.946-6.047); sICH was 9.1% in IVT and 8.7% in IAT ( $P=1.000$ ,  $RR=0.957$ , CI 0.200-4.579). Eleven patients died, nine of which were in the IVT group (16.4%) and two in the IAT group (8.7%), ( $P=0.492$ ,  $RR=1.882$ ; 95% CI: 0.440-8.045). During hospitalization, the incidence of pulmonary infection were 8.7% and 7.3% in IAT and IVT groups respectively ( $P=1.000$ ,  $RR=1.196$ ; 95% CI :0.235-6.079). No cases of deep venous thrombosis or septicemia occurred in any of the patients observed (see Table 2).

In the IAT group, DSA showed that two (8.7%) patients had a carotid occlusion, three (13.0%) patients had an anterior cerebral artery A1 occlusion, seven (30.4%) patients had middle cerebral artery M1/M2 occlusion, and eleven (47.8%) patients had a more distal artery occlusion.

In the IAT group, incidences of recanalization were: absent (TIMI-0) in one (4.3%), minimal (TIMI-1) in three (13.0%), partial (TIMI-2) in ten (43.5%), and complete (TIMI-3) in nine (39.1%). The single patient with TIMI-0 occurred as the patient's blood pressure stayed consistently above 180/100 mmHg requiring stopping thrombolytic therapy.

## DISCUSSION

The results of our study suggest that the rate of independence achieved according to mRS with IAT was significantly better at 90 days than for the patients treated with IVT ( $RR=2.66$ ; 95% CI: 1.10-7.04). No significant differences were noted in the NIHSS score after both 24 hour and 14 days post-thrombolytic treatment. No differences were noted in the incidence of symptomatic intracerebral haemorrhage (8.7% vs 9.1%), nor mortality (8.7% vs 16.4%) between the IAT and IVT groups at three months follow-up respectively.

The results of ECASS III and SITS-ISTR<sup>7,8</sup> showed that alteplase administered in patients with acute ischemic stroke could safely extend the treatment time window from 3 to 4.5 hours after the onset of stroke symptoms. In their studies, there were 52.4% and 58.0% patients who reached independence at three months. It should be noted that these provided the same results as our study which found 56.4% had reached independence at ninety days in the IVT group. The incidence of Symptomatic intracerebral haemorrhage (ECASSII definition) in the ECASS III and SITS-ISTR were 2.4% and 5.3%, lower than

the 9.1% in our study. Mortality was 7.7% and 12.7%, lower than the 16.4% found in our study. It is possible that some of these differences were related to other factors. For instance average age in our study was 66.6 ± 9.3 whereas in the ECASS it was 64.9 ± 12.2; and in the SITS it was 65. The baseline systolic blood pressure in our patients was 155.6 ± 23.4 whereas in the ECASS it was 153.3 ± 22.1 and in the SITS it was 150. Finally the percentage of patients with atrial fibrillation was 34.5% our study and only 12.7% in ECASS and 20% in SITS. Our finding support the result of a meta-analysis<sup>6</sup> that suggested a treatment time window of 4.5h was feasible for patients with anterior cerebral circulation occlusion.

Although IVT can improve patients' outcome, IVT does not benefit all patients equally, particularly those patients with severe deficiencies and larger vessel occlusion<sup>2</sup>. The occlusions of the major artery are usually accompanied with a greater thrombus burden. This situation makes it hard for the medication to reach the lesion leaving the distal divisions and cortical branches not accessible for recanalization<sup>10,16</sup>. There have been a number of studies demonstrating that intra-arterial thrombolysis is safe and effective when compared to IVT, especially in cases of middle cerebral artery and basal arterial occlusion<sup>10-13,17</sup>.

In our study, we compared IVT and IAT in patients with anterior cerebral circulation occlusion and have found that IAT had significantly improved results in the patient relevant outcome of independence at three months. However, other measures including NIHSS improvement at 24 hours and 14 days post-treatment and the incidence of haemorrhage, sICH, and mortality were not significantly different between two groups in three months follow-up.

Previous studies demonstrate that increasing age, hypertension, baseline NIHSS score, cardioembolic stroke, main stem occlusion, and early focal hypodensity on CT are associated with an increased risk of haemorrhage transformation<sup>18-21</sup>. Most anterior cerebral circulation occlusions are due to embolic occlusions, leading to main stem occlusion and serious symptoms. Recent studies have found that recanalization was one of the best predictors of good outcome after thrombolysis. It should be noted however, that incomplete recanalization may increase the rate of the haemorrhage transformation<sup>20-23</sup>. This is especially the case when delayed recanalization occurs more than six hours after thrombolysis<sup>20</sup>. In most studies, IAT treatment is longer than IVT and may delay recanalization thereby increasing the incidence of haemorrhage<sup>9,16,20,21</sup>.

In our study patients underwent IAT an average of 90 minutes after IVT, yet the incidence of haemorrhage, sICH and mortality were comparable in both groups. Moreover, as more patients reached independence it is possible that a higher recanalization rate occurred in the IAT group in comparison to the IVT group, however this outcome can only be implied as it was not assessed. In the IAT group, TIMI-2 or TIMI-3 recanalization TIMI-s were observed in 19 of 23 patients (82.6%). However, we could not confirm the conclusion since we have no DSA information of the IVT group. One angiographic-controlled pilot trial reported the rate of recanalization in major arterial occlusions with IV rt-PA. Partial or complete recanalization took place in only 10% of occluded internal carotid arteries and in 25% of occluded proximal middle cerebral arteries<sup>24</sup>.

There are some limitations to our study. First and foremost this was not a randomized trial and thus more susceptible to bias;

second, the evaluator was not blinded as to the treatment; third, patients were evaluated only by phone at three month follow-up. Fourth, the sample size was relatively small and potentially underpowered to assess for differences beyond that of the outcome for independence.

Our study does contribute to the evidence supporting the use of IAT following ischemic stroke and occlusion of anterior cerebral circulation. Whether IAT improves outcome after stroke compared with IVT and which kind of stroke should be selected for IVT or preferably IAT requires further study. A large controlled randomized trial is warranted to better address this question.

## CONCLUSIONS

The results of our study found a benefit from neurological deficit at three months following intra-arterial thrombolysis within six hours as compared to intravenous thrombolysis within 4.5 hours in patients with occlusion in the anterior circulation. No differences were found for the incidence of haemorrhage or mortality whether patients were treated with IAT or IVT.

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