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# Thrombolysis in acute stroke without angiographically documented occlusion

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**Abstract. – OBJECTIVE: The aim of this study was to evaluate the safety and efficacy of intra-arterial thrombolysis (IAT) using urokinase (UK) in acute stroke patients without angiographically-documented occlusion, and to define predictors of clinical outcome.**

**PATIENTS AND METHODS: We analyzed clinical and radiological data of acute ischemic stroke patients whose angiography did not show an arterial occlusion within six hours of symptom onset and who were further treated with IAT using UK. The primary outcome was a modified Rankin Scale (mRS) score ≤ 2 at 90 days' post procedure.**

**RESULTS: In a thrombolysis database of 263 patients, we identified 51 patients without angiographically-documented arterial occlusion who received IAT with UK within six hours of symptom onset. The median baseline NIH stroke scale measurement was 11 (range: 8-20). From symptom onset, the mean time to treatment was 4.1 ± 1.3 h (median: 4.5 h; range: 1.5-6.0 h). Immediate and dramatically clinical improvement was seen in 29/51 (56.9%) patients. One patient (2.0%) developed a symptomatic intracranial hemorrhage. At three months, 38/51 (74.5%) patients were independent (mRS ≤2), 13/51 (25.5%) patients were dependent (mRS > 3), and no patients died. No predictors of clinical outcome were identified.**

**CONCLUSIONS: IAT using UK can be a safe and efficacious therapy for the treatment of acute ischemic stroke in patients without angiographic occlusion. Approximately 75% of these patients had a favorable clinical outcome and thrombolysis-related symptomatic hemorrhage was low.**

Key Words
Stroke, Thrombolysis, Clinical outcome.

## Introduction

Approximately 20-30% of acute ischemic stroke patients with clinical deficits do not show an arterial occlusion on a cerebral angiography when performed within six hours of symptom onset[1]. About treatment decision, these patients pose a clinical dilemma. According to most protocols, intra-arterial thrombolysis (IAT) is not administered in the absence of a visible arterial occlusion[2-4]. However, recent studies[5-7] suggested that the outcomes following ischemic stroke in patients without angiographically-documented occlusion are not uniformly good, so more aggressive treatment strategies are warranted.

In the intravenous National Institute of Neurological Disorders and Stroke (NINDS) trial[8], a clinical benefit was shown in all stroke subgroups of patients, including patients with small artery disease. However, whether ischemic stroke patients with no visible occlusion on angiography would benefit from IAT is unknown. For this reason, we analyzed acute ischemic stroke patients without angiographically-documented occlusion who had been treated with intra-arterial urokinase (UK) thrombolysis. The aim of this study was to evaluate the safety and efficacy of IAT using UK in acute stroke patients without angiographically-documented occlusion and to identify clinical and stroke risk factors associated with their clinical course.

## Patients and Methods

### Patients

This is a retrospective study of acute ischemic stroke patients who presented to our institution, the First Bethune Hospital of Jilin University, from June 2004 to December 2011. The eligible population consisted of patients who underwent cerebral angiography immediately after a clinical evaluation and subsequently received a computerized tomography (CT) scan with the intention to perform IAT.

IAT was indicated for 18-to 80-year-old patients experiencing an acute ischemic stroke, within six hours of symptom onset, and with an initial National Institute of Health Stroke Scale (NIHSS) score from 8 to 25. Patients also must have had a normal

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head CT scan. Exclusion criteria were: neurologic symptoms caused by subarachnoid hemorrhage, neoplasm, septic embolism, moyamoya disease, or vasculitis; seizure at onset; rapidly improving neurologic signs at any point before IAT; history of stroke within the previous four weeks (except transient ischemic attacks or lacunar infarction); recent major surgery in the past two weeks; active or recent hemorrhage within two weeks; baseline international normalized ratio of 1.5 or greater; platelet count of $<10\times10^9$/L; uncontrolled hypertension defined by systolic blood pressure >180 mmHg and diastolic blood pressure >110 mmHg.

Our cohort was populated with patients who had a final diagnosis of stroke, received IAT with UK within six hours of symptom onset, and had no visible arterial occlusion on digital subtraction angiography (DSA).

This retrospective study was approved by the Institutional Review Board and the need for informed consent was waived.

### Endovascular Therapy

In all cases, a diagnostic four-vessel intra-arterial DSA was performed by an experienced endovascular neurologist using a 5-French (Fr) catheter and a transfemoral approach. Angiographic images were reviewed at the time of angiography and intra-arterial low-dose UK was administered to the vascular territory appropriate for symptoms, even if the patient did not show evidence of occlusion. If the suspected distribution of ischemia was referable to anterior circulation, thrombolytic agents were infused into the internal carotid artery appropriate for symptoms. If the suspected distribution of ischemia was referable to posterior circulation, thrombolytic agents were infused into the dominant vertebral artery. The maximum dose administered was 1,000,000 U, infused manually at a rate of 10,000 U per minute.

Patients were supervised at the Intensive Care Unit. All patients underwent a CT scan immediately following thrombolytic therapy. A follow-up CT or magnetic resonance imaging (MRI) was routinely carried out within three days after IAT. The neuroimaging studies were reviewed to identify the presence of new infarction and/or intracranial hemorrhage.

### Outcome Measures

All patients were screened for NIHSS score at admission. Outcomes were determined by the use of the modified Rankin score (mRS) at 90 days after the procedure. Favorable clinical outcomes were defined as a mRS score ≤2.

### Statistical Analysis

All data were analyzed using the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA). Continuous and categorical variables were presented as means with standard deviations and frequencies, respectively. Comparisons of clinical and radiological characteristics and outcomes were performed using the Fisher's exact test or *t*-test. A two-sided *p*-value of $<0.05$ was considered to be statistically significant.

## Results

In a database of 263 patients who had received IAT for acute ischemic stroke, we identified 55 patients (20.9%) with no visible arterial occlusion on digital subtraction angiography (DSA). Of these patients, 51 patients had received IAT with UK within six hours of symptom onset. A final diagnosis of stroke was made in all of these patients. Data collected from these 51 patients are the subject of this study.

The mean age of our patient cohort was 55.2 ± 10.8 years and the majority (74.5%) were men. The following risk factors were noted: hypertension (74.5%), diabetes mellitus (37.3%), hypercholesterolemia (35.3%), smoking (51.0%), alcoholism (31.4%), atrial fibrillation (5.9%), and past history of strokes/TIAs (35.3%). Presumed causes of stroke included cardiac embolism in 5/51 patients (9.8%), small-vessel disease in 34/51 patients (66.6%), and undetermined cause in 12/51 patients (23.5%).

The mean baseline NIHSS on admission was 11.1 ± 2.7 (range: 8-20). The mean time to treatment from symptom onset was 4.1 ± 1.3 h (range: 1.5-6.0 h). Thirty-six lesions (70.6%) were located in the anterior circulation and fifteen lesions (29.4%) were in the posterior circulation. The mean dosage of UK was $50.9 \pm 22.0\times10^4$ U (range: $20\text{-}100\times10^4$ U). A dramatic and immediate clinical improvement (as defined by a ≥4 point reduction in NIHSS score) was seen in 29/51 patients (56.9%). However, in 8 of these patients, their neurological status did not return to the pre-treatment level until 24 h. Of note, all of these slower-responding patients had lesions that were located in the anterior circulation. Furthermore, 3/51 patients (5.9%) developed asymptomatic intracerebral hemorrhage (hemorrhagic transformation 1) and 1/51 patient (2.0%), who developed symptomatic intracerebral hemorrhage (sICH), survived and had a mRS score of 2 at a 90-day evaluation.

All patients had a follow-up CT or MRI within three days of the procedure. This analysis showed that 3/51 patients (5.9%) had normal scans, 22/51

patients (43.1%) had a single penetrating artery infarct, 21/51 patients (41.2%) had multiple penetrating artery infarcts, 2/51 patients (3.9%) had a single cortical infarct, and 5/51 patients (9.8%) had multiple cortical infarcts.

At three months post-treatment, 38/51 patients (74.5%) were independent (mRS ≤ 2), 13/51 patients (25.5%) were dependent (mRS > 3), and no patients died. A more detailed analysis indicated that 13/51 patients (25.5%) had a mRS score of 0, 10/51 patients (19.6%) had a mRS score of 1, 15/51 patients (29.4%) had a mRS score of 2, and 13/51 patients (25.5%) had a mRS score between 3-4.

We performed univariate analyses to look for any associations between patient characteristics and clinical outcome (a good outcome was defined as mRS ≤ 2). Age, sex, vascular risk factors, baseline NIHSS score, the dosage of UK, treatment time, and finding on follow-up imaging all failed to predict clinical outcome (Table I).

## Discussion

The rates of favorable outcomes in acute ischemic stroke patients without angiographically-visible occlusion ranged from 33% to 75% in various previous studies[6,7,9-11]. One of the studies that documented a favorable outcome for 75% of its patients had a cohort with a lower median baseline NIHSS of 7 (range: 4-25)[9], compared with the higher median baseline NIHSS of 11 (range: 8-20) in the current study. Although outcomes are better for ischemic stroke in patients with arterial occlusion, acute ischemic stroke without angiographically-documented occlusion is not benign; death or disability is observed in at least one-third of the patients[5-7]. There are only a few reports[5,12] describing the outcomes of these patients who are subsequently treated with thrombolysis. In a small series including five stroke patients without visible clot on arteriography who had been treated with IAT, four of the five patients continued to have a good outcome out to three months post treatment[12]. In another series of 99 stroke patients without intracranial occlusions on Computed Tomography Angiography (CTA), 50/99 (50.5%) of the patients received thrombolysis. The mean baseline NIHSS for this cohort was 10 (range: 7-14). Intravenous tissue plasminogen activator (tPA) was administered in 49 of the patients and 1 patient received IAT. Dramatically, early clinical improvement was seen in 17/49 patients (34.0%). Only 1 patient developed sICH[5]. Therefore, the use of thrombolytic therapies in this patient population appears safe and justified.

**Table I.** Univariate analysis of the association between clinical, demographic, and radiologic features and three-month clinical outcome.

| | mRS ≤2 (n=38) | mRS >2 (n=13) | *p*-value |
|---|---|---|---|
| Age (yr), mean ± SD | 54.7 ± 11.3 | 56.6 ± 9.4 | 0.589 |
| Male, n (%) | 29 (76.3%) | 9 (69.2%) | 0.716 |
| Posterior circulation, n (%) | 14 (36.8%) | 1 (7.7%) | 0.076 |
| Hypertension, n (%) | 28 (73.7%) | 10 (76.9%) | 1.000 |
| Diabetes mellitus, n (%) | 13 (34.2%) | 6 (46.2%) | 0.515 |
| Hypercholesterolemia, n (%) | 12 (31.6%) | 6 (46.2%) | 0.502 |
| Current smoker, n (%) | 18 (47.4%) | 8 (61.5%) | 0.523 |
| Alcohol, n (%) | 12 (31.6%) | 4 (30.8%) | 1.000 |
| Atrial fibrillation, n (%) | 3 (7.9%) | 0 (0%) | 0.561 |
| Previous stroke/TIA history, n (%) | 12 (31.6%) | 6 (46.2%) | 0.502 |
| Baseline NIHSS, mean ± SD | 11.1±2.9 | 11.5±1.9 | 0.640 |
| UK dose (×104 U), mean ± SD | 50.0±21.7 | 53.5±23.4 | 0.629 |
| Treatment time (hrs), mean ± SD | 4.1±1.4 | 4.3±1.3 | 0.521 |
| Single PAI, n (%) | 18 (47.4%) | 4 (30.8%) | 0.348 |
| Multiple PAI, n (%) | 13 (34.2%) | 8 (61.5%) | 0.109 |
| Single CI, n (%) | 2 (5.3%) | 0 (0%) | 1.000 |
| Multiple CI, n (%) | 4 (10.5%) | 1 (7.7%) | 1.000 |
| Normal follow-up scan, n (%) | 3 (7.9%) | 0 (0%) | 0.561 |

NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale score; TIA, transient ischemic attack; PAI, penetrating artery infarct; CI, cortical infarct; NS, not significant.

The present work investigated 51 acute ischemic stroke patients without angiographically-documented arterial occlusion who received IAT with UK within six hours of symptom onset. A marked and immediate clinical improvement (as defined by a ≥4 point reduction in NIHSS score) was noted for 29/51 (56.9%) of the patients. By three months, a favorable outcome was seen in 41/51 patients (74.5%), 14/51 patients (25.5%) were dependent (mRS > 3), and no patients had died. In our cases, the majority (74.5%) had a favorable clinical outcome, despite the fact that most were in poor condition at the initiation of IAT. Only one patient (2.0%) developed sICH. The lower incidence of IAT-related sICH in our study could also be explained by the lower dose of UK that was used (median: $50\times10^4$ U; range: 20-$100\times10^4$ U).

There are several potential mechanisms that could contribute to the incidence of acute ischemic stroke in the absence of demonstrable arterial occlusion. The two most likely reasons are small vessel occlusion in a nonvisible artery or spontaneous lysis of an occluding thrombus. Several authors have previously argued that a lysis of the occluding thrombus would have already occurred in stroke patients who have a clinical deficit but do not have an angiographically-documented arterial occlusion. In this setting, thrombolytic therapy presents a risk of intracerebral hemorrhage without any added benefit[3, 13-15]. However, a percentage of patients with complete large vessel spontaneous recanalization may have distal occlusions that are not visible on DSA, and who may suffer a high rate of symptomatic ischemic stroke and/or disability without any treatment. Indeed, in the NINDS trial[8], the benefit of intravenous thrombolysis was observed in patients with small vessel disease. On the other hand, our data suggest that thrombolysis-related symptomatic hemorrhage was low in our population. Thus, it is unjustified to prevent all stroke patients that do not have an angiographically-revealed artery occlusion from receiving thrombolytic therapy.

## Conclusions

The present retrospective work showed that IAT using UK is a safe and efficacious treatment for acute ischemic stroke patients without an angiographically-revealed artery occlusion. Nearly 75% of these patients had a favorable clinical outcome and thrombolysis-related symptomatic hemorrhage was low. Further studies are needed in this population to confirm the results of the present study and to define parameters associated with clinical outcome.

### Conflict of Interest

The authors declare no conflicts of interest.

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