Evaluation of safety and efficacy of intra-arterial thrombolysis for acute stroke in patients 80 and older − two center study

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[Abstract] Object The purpose of this study was to evaluate the feasibility, safety and efficacy of very elderly patients (≧80 years) with acute ischemic stroke treated with intra-arterial thrombolytic therapy. **Method** The characteristics and clinical outcome of patients aged ≧ 80 years (n =21) were compared retrospectively contemporaneous patients aged < 80 years (n =65) from a registry of consecutive patients treated with intra-arterial thrombolysis and control group who aged ≧ 80 years and did not received thrombolytic therapy (n =50). **Results** There were no significant difference in favorite recanalization rate, short-term outcome and incidence of symptom intracranial hemorrhage between the very elderly and younger cohorts who received thrombolytic therapy (P=0.528, P=0.102, P=0.353). The incidence of symptom intracranial hemorrhage in the very elderly patient group was lower than that of normal age patient group (42.9% versus 50.8%, P=0.042), however, which is higher than that of the control group (42.9% versus 16%, P=0.017). The mortality of very elderly group who received thrombolytic therapy was similar to that of the control group (23.8% versus 28%, P=0.816), which was higher than that of younger cohort group (23.8% versus 10.8%, P=0.034). **Conclusions** There were relatively high feasibility, safety and efficacy in very elderly patients (≧80 years) with acute ischemic stroke treated with intra-arterial thrombolytic therapy. These findings demonstrate that the use of intra-arterial thrombolytic therapy in very elderly patients should not be avoided but pursued advisably.

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Introduction

Age is the most important unmodified risk factor of actue ischemic stroke (AIS), and the mortality rapidly increased with age[1]. The treatment of very elderly patients with AIS presents physicians with a unique and increasingly important challenge. Brown et al reported that persons aged 85–94 years experience a 2-fold higher incidence of AIS compared with persons aged 65–74 years and a 26-fold higher incidence compared with persons aged 45–54 years[2]. The old person is rapidly growing worldwide. The person aged 65 years and older account for 8.87% of all population in china[3]. For AIS, thrombolysis remains the only proven effective therapy, despite hemorrhagic complications. Schwark et al found Among the patients with AIS received IV recombinant tissue plasminogen activator within 3 hours after symptoms onset, the incidence of symptomatic hemorrhage in patients ≧80 is notably higher than that of in patients <80[4]. However, Intra-arterial thrombolysis (IAT) has the merit of high rate of recanalization and low incidence of hemorrhage related with thrombolysis. It is unclear that if very elderly patients (≧80 years) is suitable for IA thrombolytic therapy. The aim of study was to compare the efficacy and safety of acute ischemic stroke patients aged ≧80 years treated by IAT with those younger than 80 years of age.

Methods and subjects

From May 2006 to May 2010, 91 consecutive patients (44 women and 56 men) with AIS were treated with IAT using urokinase or rt-PA in the first affiliated hospital of ZhengZhou university and the sixth hospital of ShangHai JiaoTong university. Five of these patients were lost in 9o-day follow-up. Therefore, a total of 86 patients (52 men and 34 women) were chosen in this study. Three groups was classified according age: very elderly patient group (≧80 years), younger cohort groups (<80) and control group. There were 21 and 65 patients in two groups respectively. 50 patients (≧80 years) with AIS who did not receive IAT because the admission time was from six hours to twenty four hours after symptom onset. The baseline characteristic of these patients were shown in table 1.

Inclusion criteria of IAT : (1) neurological signs indicate ischemic lesion in the anterior circulation; (2) 4≤baseline NIHSS score ≤ 24; (3) 3 hours≤ the

time window of IV/IAT or IAT ≤6 hours; (4) patients aged ＜ 80 years; (5) CT excluded intracranial hemorrhage or significant mass effect.

Exclusion criteria of IAT: (1) symptomatic ischemic stroke within 6 weeks, (2) head trauma within the previous 90 days, (3) surgery within 90 days, (4) biopsy involving a major organ within 2 weeks, (5) a history of intracranial hemorrhage, (6) a clinical presentation suggestive of subarachnoid hemorrhage or septic embolism, (7) gastro-intestinal or any serious hemorrhage within 3 weeks (8) Systolic BP＞185 mmHg or diastolic BP ＞110 mmHg despite the use of IV nitroprusside or labetalol, and (9) Laboratory exclusion criteris: Protime ＞15 seconds; platelets ＜ 100,000/mm3; Blood glucose＜2.8 or ＞22 mmol/L.

Bilateral internal carotid artery and the vertebral basilar system angiography were performed via femoral route to evaluate the site and extent of thrombus and collateral blood flow. Occlusion and recanalization were graded by according to Mori grade [70]. After identification of the occlusive artery, a 6F guide catheter was advanced into the lesion-related side common carotid artery or internal carotid artery. Heparin at a dose of 500 U/hour was continuously infused in the catheter until the end of the procedure. A microguidewire and microcatheter were used to traverse the occluded segments several times in an attempt to disrupt the clot, and then the microcatheter was embedded into the clot. UK (60,000-120,000 unit) or rt-PA (0.5mg/kg) was administered through microcatheter. Mechanical disruption of thrombus with the microguidewire and microcatheter was fitfully attempted during the procedure. Diagnostic angiography through the guide catheter or microcatheter was performed at 10-minute intervals. Termination of the IA treatment procedure occurred if there was: (1) achievement of thrombolysis in Mori grade 4; (2) beyond the 6 hours from stroke onset.

All patients underwent nonenhanced head CT scanning within 24 hours of thrombolysis and immediately upon neurologic deterioration. After thrombolytic therapy, all patients were admitted to neuro-intensive care units for close monitoring of vital signs. No antiplatelet agents and anticoagulation were administered within 24 hour after symptom onset. Heparin was reversed with protamine immediately if parenchymal hyperdensity shown on CT. 24 hours later, all patients without sICH were administered aspirin 100 mg orally daily for at least 6 months.

Neuroradiological and Outcome Evaluation

Severity of neurological deficit was assessed at admission and 7 days after onset by a neurologist using the NIHSS. Early neurologic improvement was defined as an improvement NIHSS score by four or more points on the NIHSSS between baseline and 7 days or a NIHSSS of 0 to 1 at 7 days, although this was not recognized as the end point of the study [15]. Arterial patency was rated by the thrombolysis in Mori grade in which 0 indicates no perfusion, 1 is minimal reperfusion, 2 is reperfusion of less than 50% of the territory of the occluded artery, 3 is reperfusion of more than 50% of the territory of the occluded artery, and 4 is complete reperfusion. We defined Mori grade 2-4 as recanalization, Mori grade 3-4 as good recanalization, and Mori grade 0-2 as poor recanalization. Symptomatic ICH was defined as neurological worsening ⩾ 4 points in NIHSS and attributable to cerebral hemorrhage shown on CT. Clinical outcome was assessed with mRS at 90 days which was grouped into two categories: good outcome (mRS score, 0–2) for those patients who were functionally independent, poor outcome those who were dependent (mRS score, 3–5), and death corresponds to mRs score of 6 [1]. The investigators were not blinded to the baseline NIHSS scores, angiographic results and clinical outcome.

Statistical Analysis

Descriptive and frequency statistical analysis were obtained and comparisons were made using the statistical software SPSS 15.0. For calculation of significant differences among the three groups were analyzed with variance analysis, the chi-square test respectively, the Mann-Whitney U test and logistic regression analyses. Ninety-five percent confidence intervals were calculated for odds ratios and for relative risk. The following variables were analyzed: age, sex, baseline NIHSS scores, early neurologic improvement, time from symptom onset to thrombolysis, mortality, incidence of sICH and good outcome. A probability value of $P<0.05$ was considered statistically significant. All values are presented as means ±SD or as medians

Results

General Characteristics

Among 86 patients who received IAT, 21 patients were older than 80 years (the mean age was 83.4±3.1, from 80 to 89 years), 65 patients were younger than 80 years (the mean age was 61.2±8.7 years, from 36 to 79 years). The mean age of 50 patients in control group was 82.3±3.7 years，from 80 to 92 years. There were significant difference in age and incidence of coronary disease among the three groups (p=0.000). Sex and risk factors including hypertension, diabetes, TIA and atrial fibrillation did not differ among these groups. Baseline patient characteristics for the 2 groups are presented in Table 1.

There were 7 patients (33.3%) whose NIHSS score dropped by 4 points in very elderly patients

group as compared with 35 patients (53.8%) in younger cohort group (p=0.528). Good recanalization rates (Mori 3-4) were 42.9% which is lower than that of younger cohort group (50.8%), but there were no significant difference between the two group (p=0.102). The incidence of sICH in very elderly patients group (19.0%) was notably higher than that of young cohort group (12.3%， p=0.353)and control group (6%， p=0.034). 42.9% of very elderly patients group had a favourite outcome (mRS score of 2 or less) at 90 days after stroke as compared to 50.8% of young cohort group ((p=0.042), which was higher than 16% of control group (p=0.017). Mortality was 23.8% in very elderly patients, which was higher than that of younger patients (p=0.034), however was lower than that of control groups (p=0.816). the result indicated that the clinical outcome of very elderly patients who received IAT was better in comparison with similar patients who did not receive IAT, nevertheless, which was worse than that of younger patient who received IAT (Table 2,3).

Table 1. Baseline Characteristics of three groups

	Intra-arterial thrombolysis		Congrol group
	≧ 80 years (n=21)	< 80 years (n=65)	≧ 80 years (n=50)
Age (year)*	83.4	61.2	82.3
Sex, male	61.9%	60.5%	64.0%
Hypertension	66.7%	50.8%	62.0%
Diabetes	61.9%	40.0%	56.0%
TIA	28.6%	12.3%	18.0%
Atrial fibrillation	28.6%	23.1%	26.0%
Coronary artery disease *	71.4%	26.2%	56.0%
Baseline NIHSS	15.6	14.5	17.3
Location of infarct			
Anterior circulation	85.7%	86.2%	92.0%
Posterior circulation	14.3%	13.8%	8.0%
Thrombolytic agent			
urokinase	15 (71.4%)	51(80.5%)	
r-tPA	6 (18.6%)	14(21.5%)	

There were no significant difference in baseline characteristics among the three groups except for age and coronary disease. (p>0.05)

*** there were** significant difference in age and coronary disease between the two groups which received IAT(p<0.05), however, no significant difference in all baseline characteristics between the two groups whose patients were older than 80 years(p>0.05).

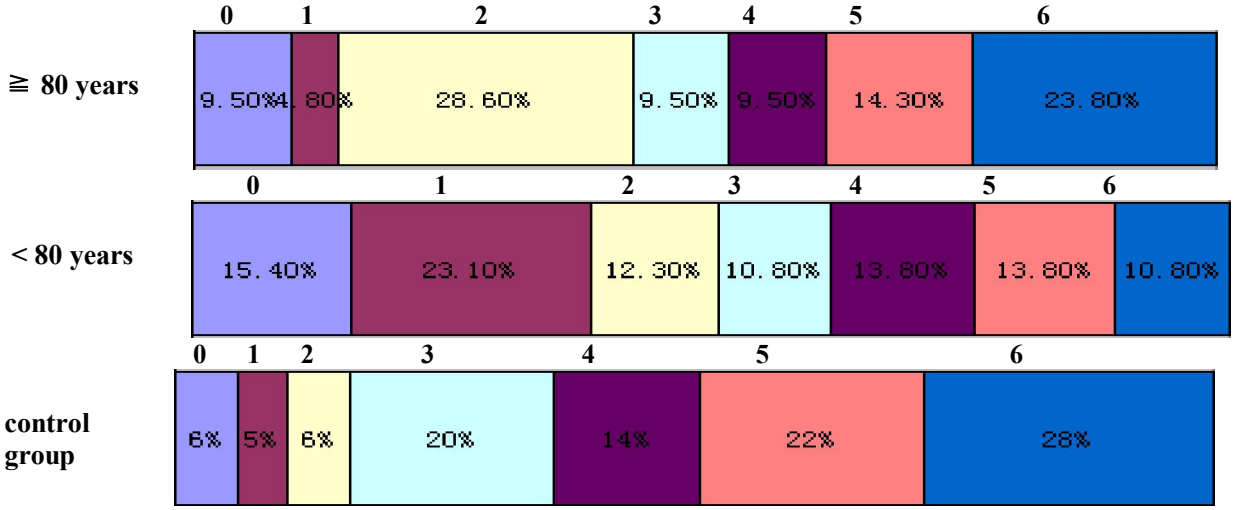
Table 2. The clinical outcome of the three groups

	Intra-arterial thrombolysis		Control group
	≧ 80 years (n=21)	< 80 years (n=65)	(n=50)
Early neurologic improvement (NIHSS improvement ≧4)	33.3%	53.8%	
Good recanalization after IAT （Mori grade 3-4）	42.9%	50.8%	
Symptomatic ICH	19.0%	12.3%	6.0%
good outcome（mRS 0-2）	42.9%	50.8%	16.0%
Mortality	23.8%	10.8%	28.0%
Complication of femoral artery puncture	1(4.8%)	4(6.2%)	

Table 3. Comparison of the clinical outcome among the three groups

	≧ 80 years and < 80 years		≧ 80years and control group	
	χ2 值	*P* 值	χ2 值	*P* 值
Good recanalization	0.398	0.528		
Early neurologic improvement	2.673	0.102		
Symptomatic ICH	0.863	0.353	4.491	0.034
good outcome	4.140	0.042	5.858	0.017
Mortality	4.472	0.034	0.085	0.816

Chart 1. Modified Rakin scale score at 90 days in different groups



Discussion

Stroke primarily affects an elderly population. Brown reported that more than half of the strokes in this population affected subjects aged ≧75 years and nearly one quarter affected subjects aged ≧85 years[2]. A Multicenter Cohort Study Across Canada found that 38% of hospitalized patients with an ischemic stroke occurred in individuals aged 80 or older[5].

In 2007, Kim et al firstly compared the safety and efficacy between very elderly patients (≧ 80 years) and younger patients (< 80 years) with AIS who all received IAT[6]. They found significant differences in recanalization rates and symptomatic ICH could not be detected between the very elderly and younger patients, the good outcome was worse in the former compared to the latter. However, one limitation of this study was no comparison of safety and efficacy between very elderly patients treated with IAT and without IAT. Our study not only compare the safety and efficacy of AIS patients (≧ 80 years) treated with IAT and that of younger patients, but also designed a control group of patients 80 years and older who did not receive IAT to provide relative estimates of treatment benefit.

This pilot study demonstrates the feasibility of treatment of very ischemic stroke patients (≧ 80 years) treated with IAT. Despite this success, clincial outcome of very elderly patients was not improved compared with that of younger patients, but inference is limited because of a small numbers of patients, an excess of adverse events unrelated to treatment assignment in the very elderly group. The safety of a two groups which received intra-arterial thrombolysis was acceptable in this small pilot study. The rate of symptomatic ICH and recanalization in younger group was 12.3% and 50.8%, which were similar to the rate of the PROACT II study and previous IA cohort series report[7, 8]. A higher rate of symptomatic ICH and lower proportion of recanaliation and good clinical outcome accomplished in very elderly patients in comparison with younger patients and Kim study. In a study involving 33 ischemic stroke patients who were 80 years or older, all patients were treated with intra-arterial thrombolytic therapy. Kim and coworkers emphasized the feasibility of IAT for very patients with AIS and demonstrated that the rate of recanalization, symptomatic ICH , good clinical outcome and mortality at 3 months were 79% were 79%,7% , 44% and 43% sequently. We think the differences may be related with discrepancy of race, baseline characteristics, time to treatment, thrombolytic drugs and dosage of drug.

Ever since thrombolysis was first administered to

stroke patients in the 1950s[9]. Symptomatic ICH associated with cerebral revascularization therapy has deterred its use. Kidwell thought the risk factors for symptomatic ICH were age, high NIHSS Score, long time to treatment, hypertension, diabetes, leukoaraiosis, severe ischemia and high dose thrombolytic therapy[10]. Several studies have identified age as an independent risk factor for intracerebral hemorrhage after intravenous fibrinolysis, administered for both myocardial and cerebral ischemia[11-13]. Nevertheless, a meta-analysis conducted by Mijderwijk and coworkers found age is not a risk factor for symptomatic intra-cerebral hemorrhage (sICH) for acute stroke patients after intra-arterial thrombolysis[14]. This finding contradicted our result. In our study, the rate of symptomatic ICH in patients aged ≧80 years were apparently higher than patients aged < 80 years. Trouillas reported that high incidence of symptomatic ICH in very elderly patient may be connected with cerebral amyloid angiopathy, fragile vasculature and delayed half-life period of thrombolytic drug[15]. We approve of Trouillas's view.

In our study, compared to patients aged < 80 years, the lower rate of good functional outcome and higher mortality rate observed in the patients aged≧80 years after IAT. We think a variety of factors probably contribute to reduced functional outcome, despite successful reperfusion in the elderly, (1) a higher frequency of prior stroke/TIA, higher frequency of prestrike comorbid conditions and poststroke medical complications. (2) impaired collateral circulation, Collateral circulation is believed to salvage parts of the ischemic territory and, thus, positively affect eventual functional outcome. In the elderly population, the ability to form collateral pathways may be acutely decreased. (3) reduction of multi-organ function. It's important to note that the good clinical outcome of very elderly patients who received IAT was better than people of the same age who did not receive IAT. This finding support the concept that the very elderly ischemic stroke patients are worth being treated with IAT, because it can remarkably improve the clinical outcome and reduce the mortality rate. With the introduction of combined intra-venous and intra-arterial thrombolytic therapy, mechanical recanalization and clot retrieval device such as Penumbra and Merci, the efficacy of interventional therapy will be improved.

Because of the small sample size, our results are preliminary and preclude us from reaching completely generalizable conclusions. Large-scale prospective randomized studies in future are required to confirm the results of this study.

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