CNS Neuroscience & Therapeutics

CLINICAL GUIDELINE

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Consensus Statement on the Use of Intravenous Recombinant Tissue Plasminogen Activator to Treat Acute Ischemic Stroke by the Chinese Stroke Therapy Expert Panel

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SUMMARY

Background: The last update of the consensus statement on intravenous recombinant tissue plasminogen activator (IV rt-PA) for acute ischemic stroke (AIS) by the Chinese Stroke Therapy Expert Panel was published in 2006. Great progress has been made since then. **Aim:** To provide another update on the new knowledge of IV rt-PA for AIS since 7 years ago. **Method:** In summer of 2012, the Chinese Stroke Therapy Expert Panel was reconvened. New publications on the use of IV rt-PA for AIS were reviewed. In addition, all newly published consensus and guidelines from other countries were reviewed. The 2006 version of Chinese Consensus was then updated. **Results:** There is now clinical evidence to support the use of IV rt-PA between 3 and 4.5 h after the onset with several exclusion criteria. More studies are needed to provide the evidence for IV rt-PA use beyond 4.5 h. There is benefit giving IV rt-PA within 3 h to patients who are older than 80 and in patients with ongoing atrial fibrillation. Patients with INR<1.7 while on warfarin, minor strokes, rapid improving strokes and severe strokes should be treated and can all be benefited from IV rt-PA. **Discussion:** Since IV rt-PA was initially recommended in 1996, there is now more evidence support its use, efficacy and safety. The treatment time window is also being expanded. More public education on stroke recognition are needed so many stroke patients may benefit from the treatment. **Conclusion:** The 2013 version of Chinese IV rt-PA consensus contains the most up-to-date information on the use of IV rt-PA for AIS. It will be a useful tool and guideline to provide appropriate thrombolytic therapy to stroke patients who meet the criteria.

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Introduction

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is currently the most effective therapy for acute ischemic stroke (AIS). Since the last consensus statement by the Chinese Stroke Therapy Expert Panel in 2006 [1], great progress has been made in the area of IV thrombolysis for AIS. In the summer of 2012, the panel reconvened and updated the original consensus.

The Clinical Evidence of IV rt-PA for AIS

Selecting Stroke Patients for IV rt-PA by Clinical Manifestations and Plain Computer Tomography (CT) of Brain

Within 3 h of Onset

In 1995, the National Institutes of Neurological Disorders and Stroke (NINDS) trial reported that IV rt-PA was safe and effective

to treat AIS [2]. In 2004, a meta-analysis of the NINDS study, European Cooperative Acute Stroke Studies (ECASS-I and ECASS-II), and Study on Alteplase Thrombolysis for Acute Noninterventional Therapy Ischemic Stroke (ATLANTIS-A and ATLANTIS-B) confirmed the benefits of IV rt-PA within 3 h, and its use significantly improved the outcome compared with placebo groups. The odds ratio (OR) within 1.5 h and between 1.5 and 3 h was 2.81 (95% CI 1.75–4.50), 1.55 (95% CI 1.12–2.15), respectively [3]. Furthermore, European and Chinese thrombolysis registry studies also offered more evidence supporting the use of IV rt-PA for AIS within 3 h of onset [4,5]. A meta-analysis on thrombolysis treatment in 2012 offered another confirmation that IV rt-PA significantly increased the survival and nondisability rate in the thrombolysis group (OR 1.53, 95% CI 1.26–1.86) [6].

Between 3 and 4.5 h of Onset

In 2004, a meta-analysis provided some preliminary efficacy of IV rt-PA (favorable prognosis OR 1.40, 95% CI 1.05–1.85) [3]. In 2008, the ECASS-III study provided more convincing clinical evidence: among 821 patients treated within 3–4.5 h after onset, IV rt-PA improved 3-month favorable outcome (OR 1.34%, 95% CI 1.02–1.76) except in patients who were older than 80 and had more severe strokes [NIH Stroke Scale > 25], imaging manifestation of massive cerebral infarction, and past history of stroke along with diabetes [7]. The subsequently published China Thrombolysis Registry Study [5], International Thrombolysis Register Study [8] and a pooled analysis in 2010 [9] provided further evidence that IV rt-PA within 3–4.5 h is beneficial.

Within 4.5–6 h after Onset

ECASS-I, ECASS-II, and ATLANTIS-A with the expanded treatment window to 6 h after onset as well as ALTANTIS-B study with the expanded treatment window to 5 h showed no benefit [3]. The pooled analysis of NINDS, ECASS, ATLANTIS, and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) showed that it would be harmful to give IV rt-PA after 4.5 h of onset if the treatment decision was based on clinical manifestation and plain CT of brain [9]. More recently, International Stroke Trial-3 (IST-3), the largest scale of international multicenter, randomized and controlled, open label study of 3035 patients showed that the thrombolysis group had no difference in disability survival rate (primary endpoint) after 6 months comparing with the placebo group. However, in the IV rt-PA group, the 6-month survival rate and favorable prognosis (secondary endpoint) increased significantly (OR 1.26, 95% CI 1.04–1.53); symptomatic intracranial hemorrhage (sICH) increased significantly (7% vs. 1%, OR 6.94, 95% CI 4.07–11.8), and the case-fatality rate within 7 d increased significantly (11% vs. 7%, OR 1.60, 95% CI 1.22–2.08). On the other hand, the case-fatality rate from the 7th day to the 6th month decreased significantly. Therefore, the 6-month case-fatality rates in 2 groups were the same (27%). Further subgroup analysis showed that IV rt-PA given less than 3 h after onset had clear benefits, while the benefit of treating over 3 h after onset had no statistical significance [10]. The newest meta-analysis after the publication of IST-3 (including 12 IV randomized and controlled thrombolysis studies) had similar conclusion to the IST-3 study results [6]. In summary, further studies are needed to prove the benefit of treating AIS with IV rt-PA between 4.5 and 6 h.

Recommended Dose of IV rt-PA

Most randomized and controlled studies and registry studies use 0.9 mg/kg (Max 90 mg) to calculate the total dose, with 10% given as an initial bolus and the remainder infused over 1 h. Japanese Thrombolysis Registration Study used 0.6 mg/kg to calculate IV rt-PA dose and reported that this dose range was safe and effective for Japanese patients [11,12]. However, this study was not placebo-controlled. Recently, a meta-analysis of IV rt-PA in Far East Asia including the two aforementioned Japanese thrombolysis studies showed that the efficacy of 0.9 mg/kg was better than that of 0.6 mg/kg with similar bleeding risk in both dose groups [13].

Bleeding Risk after IV rt-PA

Bleeding risk, including ICH and extracranial hemorrhage, will increase after rt-PA treatment. ICH is usually categorized into asymptomatic and symptomatic [2–10,14], or hemorrhagic infarction (punctate bleeding inside infarcted area) and parenchymal hematoma on brain imaging [15–17]. sICH usually carries a poor prognosis, especially for those with NIHSS increase ≥4 and parenchymal hematoma-II type (hematoma > 1/3 of the infarction area, accompanied with obvious mass effect), suggesting a delayed recanalization [2–10, 14–18]. Hemorrhagic infarction and parenchymal small hematoma may not always bring poor clinical prognosis, and it is possible that early recanalization and better prognosis are actually possible. [14–18]. Although IV rt-PA increase the risk of severe bleeding, case-fatality rate may not increase in general, and instead, the rate of mortality and disability may decrease significantly [2–10].

There are a few tools developed to predict bleeding risk after IV rt-PA, such as hemorrhage after thrombolysis (HAT) score [19], safe implementation of thrombolysis in stroke (SITS) score [20] and SEDAN score [21]. However, these scales still need to be validated by prospective studies. At present, it is not recommended that these scales be used for the purpose of excluding patients from getting IV rt-PA.

IV rt-PA for AIS under Special Circumstances

Patients >80 Years Old

In early IV rt-PA studies, patients >80 years old were excluded, but there were clinical reports that these older patients could still be benefited from IV rt-PA if given within the time window (≤3 h). An analysis of 1585 thrombolytic patients (21% of them >80 years old) in 2010 and a meta-analysis of 13 cohort studies (764 cases aged >80 years old) in 2011 indicated that, although overall patients >80 years old had worse prognosis after IV rt-PA than the younger ones, they still had better prognosis than those who did not receive IV rt-PA, without significant increased risk of sICH [22,23]. In IST-3, 53% of the patients were >80 years old, and the subgroup analysis showed similar benefits from IV rt-PA in two age groups; however,

only patients within 3 h after the onset were beneficial from IV rt-PA thrombolysis [6,10].

Atrial Fibrillation (AF)

AF is one of the commonest causes of cardioembolic stroke, with a tendency of causing severe stroke or hemorrhagic transformation. However, none of the above clinical thrombolysis trials considered AF as an exclusion criterion, in fact, about 20% of the studied patients had AF, and AF or cardioembolic stroke was not found to be an independent risk factor for ICH after IV rt-PA [6,8,14–22]. In NINDS trial, AF combining with baseline NIHSS > 17 points predicted poor prognosis [24], but IV rt-PA group still had better prognosis than the control group [25,26]. In the recent IST-3 study, patients with AF obtained at least the similar benefit in non-AF patients from IV rt-PA [10].

IV rt-PA and Anticoagulation or Antiplatelet Therapy

In all published IV rt-PA trials, oral or systemic anticoagulation is a contraindication but not antiplatelet drugs. Recently, two large cohort studies (Registry of the Canadian Stroke Network and American Heart Association Get With The Guidelines-Stroke Registry, AHA-GWTG-Stroke) showed that IV rt-PA within 3 h of onset for AIS patients taking warfarin with an international normalized ration (INR) < 1.7 were safe and may reduce the risk of poor functional outcome [27,28].

Minor Stroke and Rapid Improving Strokes

Data from AHA-GWTG-Stroke showed that about 1/3 of minor strokes or rapid improving strokes will have long-term poor outcomes [29]. All previous rt-PA trials excluded rapid improving strokes (NIHSS decrease ≥4 point). There are currently 5 different kinds of minor strokes. NINDS trial suggested that the risk-benefit ratio for IV rt-PA in minor-stroke patients favors treatment in eligible patients [30]. However, there were only 58 cases with NIHSS < 5 points in NINDS trial. Among them, 42 patients who received IV rt-PA showed no obvious benefits as compared to the other 16 patients received placebo. In addition, no patient with isolated motor symptoms, isolated facial droop, isolated ataxia, dysarthria, isolated sensory symptoms, or NIHSS of 0 point was included [31]. The thrombolysis registration study showed that patients with NIHSS < 5 points had relatively low risks of sICH after receiving IV rt-PA within a time window of 3–4.5 h [8]. Other small clinical observation studies also suggest that patients with NIHSS of 1–5 points and rapid improvement had no more increased risk of sICH but yet somehow may benefit after IV rt-PA [32].

Severe Strokes

There was no definite upper limit of NIHSS score in NINDS study, however, stroke patients with NIHSS > 20 points were at high risk of sICH [14]. Other thrombolytic studies demonstrated an increased risk of ICH without any strong correlation to parenchymal hematoma in patients with high NIHSS score and early signs of massive infarction in baseline CT scan (dense middle cerebral artery sign, ventricular compression, cortical sulci shallowing) [19–21]. ECASS-III designated that NIHSS > 25 points and early imaging signs of massive infarction (accumulatively over 1/3 of arterial areas in brain) as the criteria for severe stroke and excluded them from getting IV rt-PA [7]. However, a meta-analysis of NINDS, ECASS-I, ECASS-II, and ATLANTIS found that IV rt-PA still had equal benefit in patients with NIHSS > 20 points to those with NIHSS < 20 points. The analysis also found that NIHSS was not an independent risk factor for parenchymal hematoma-II [3].

Thrombolysis Between 3 and 9 h with the Guidance of Multimodal Imaging Technology

Currently, there is not enough evidence supporting such practice [33–35], further studies are ongoing [36].

IV rt-PA for Acute Basilar Occlusion

There is currently no evidence from any randomized and controlled study on this application. International multicenter prospective registration studies and a meta-analysis indicated that early thrombolysis may have a favorable benefit/risk ratio, and IV rt-PA is not worse than intra-arterial thrombolysis. The time window for thrombolysis may be expanded moderately, but in general, the sooner the better [37,38].

Standardizing IV rt-PA and Increase the Use of Thrombolysis for Eligible Patients

Blood Pressure and Blood Glucose Management

Hypertension and hyperglycemia are risk factors for poor prognosis and developing sICH after rt-PA [2,3,10,14]. Systolic blood pressure > 185 mmHg (1 mmHg=0.133 kPa) or diastolic blood pressure > 110 mmHg are contraindications for thrombolysis. Blood pressure (BP) should be controlled below the recommended level before and after treatment. However, aggressive BP lowering is not recommended as it may reduce the overall perfusion of the penumbra and worsen the outcome. For hyperglycemia, euglycemic state is recommended.

Antiplatelet Therapy after Thrombolysis

All thrombolytic studies did not allow any antiplatelet or anticoagulation therapy until 24 h after thrombolysis [2–10]. The antiplatelet therapy should begin 24 h after thrombolysis without the necessity of repeating a CT of brain if the patient is clinically unchanged.

Standardize IV rt-PA

The postmarket data on rt-PA suggest case-fatality rate is related to nonstandard use of IV rt-PA. According to thrombolysis registration study, hospital case-fatality rate is inversely related to the number of patients receiving IV rt-PA. Education on how to use IV rt-PA should be carried out to ensure its appropriate usage and therefore produce similar outcome as those treated in the clinical trial [4,5].

Reduce Prehospital and In-Hospital Delay and Increase the Use of IV rt-PA

Studies during the Chinese "11th Five-Year" plan indicated that only 16% of stroke patients arrived at the hospital within 3 h after onset, and 1.3% received IV rt-PA. The sooner the patient arrived, the higher the chance of receiving IV rt-PA. Comparing the key performance indicator of stroke treatment, the gap is the largest between China and USA on the use of IV rt-PA. For stroke patients arrived at the hospital within 2 h of onset, only 9% chance was present for Chinese AIS patients to receive IV rt-PA, while American AIS patients had 70% chance. The door to needle time (DNT) in China was long (average 115 min), and the time from CT to rt-PA was as long as 86 min. Only 7% of thrombolytic patients had <60 min DNT comparing with 27% in USA [39,40]. In the AHA-GWTG Stroke program that included 25504 IV rt-PA cases, patients treated with DNT ≤ 60 min had lower case-fatality rate and sICH comparing with those treated with DNT > 60 min [39].

Recommendations from the Expert Panel

1 IV rt-PA is recommended to treat eligible patients with AIS within 4.5 h of onset. The treatment decision can be made based on the clinical manifestation and plain CT of brain. The earlier IV rt-PA is given, the more benefits and less risk will be for the patient (Level I recommendation, Level A evidence) (Appendix 1).
2 AIS patients older ≥80 who is eligible for IV rt-PA. Older patients can still benefit from the treatment (Level II recommendation, Level B evidence).
3 IV rt-PA is indicated in eligible AIS patients with AF or other cardioembolic causes (Level II recommendation, Level B evidence).
4 In AIS patients on oral anticoagulant upon presentation, IV rt-PA is indicated if INR<1.7 (Level III recommendation, Level C evidence).
5 AIS patients with minor symptoms (Level II recommendation, Level B evidence) and rapid improvement (Level III recommendation, Level C evidence), IV rt-PA is still indicated.
6 AIS patients with severe strokes (NIHSS > 25 points, or imaging display of evidence of early massive cerebral infarction), IV rt-PA should be cautiously considered (Level III recommendation, Level C evidence).
7 In patients with acute basilar artery occlusion, there is no set time window for IV rt-PA and such therapy can be considered in addition to intra-artery thrombolysis. NIHSS scores are unreliable (Level IV recommendation, Level D evidence).
8 More studies are needed to provide further evidence for using multimodal imaging technology to select AIS patients for IV rt-PA at a later time window (Level IV recommendation, Level D evidence).
9 The recommended dose for IV rt-PA is 0.9 mg/kg and the maximal dose is 90 mg, with 10% given as an initial bolus and the remainder infused over 1 h (Level I recommendation, Level A evidence).
10 Hypertension and hyperglycemia should be gently controlled in AIS patients who receive IV rt-PA. The blood pressure before and after thrombolysis should be controlled below 185/110 mmHg (Level II recommendation, Level B evidence); the goal of blood glucose should be at the level recommended by the Chinese Guideline for Acute Ischemic Stroke (Version 2010) (Level IV recommendation, Level D evidence).
11 Antiplatelet therapy started 24 h after thrombolysis is recommended (Level I recommendation, Level A evidence). If a patient developed sICH or parenchymal hematoma formation, antiplatelet agent should be stopped. No special intervention is needed for patients with asymptomatic hemorrhagic transformation or hemorrhagic infarct, and standardized use of antiplatelet drug should be maintained (Level I recommendation, Level A evidence).
12 If neurological deterioration happened, brain CT should be carried out to confirm or exclude the sICH (Level I recommendation, Level A evidence), and further work ups are recommended to define the cause and determine the method of treatment (Level IV recommendation, Level D evidence).
13 IV rt-PA should be administered by trained personnel, and the guideline should be followed (Level II recommendation, Level B evidence).
14 There is a need to perform more public education on stroke, integrate prehospital first aid system, encourage patients or citizens to use "120" emergency system, and facilitate emergency care personnel to use simple stroke screening scale. The purpose of the educational campaign is to reduce prehospital delay. In-hospital stroke standard emergency management system should be established in medical centers. AIS patients arriving at a hospital within the time window, IV rt-PA should be considered. The decision on giving rt-PA can be determined based on the clinical manifestation and plain CT of brain. The goal of DNT is <60 min (Level III recommendation, Level C evidence).

Conflict of Interest

The authors declare no conflict of interest.

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Appendix

This consensus uses the recommendation and evidence levels described in the 2010 version of Chinese Cerebrovascular Disease Guideline.

1 Strength of recommendations (4 levels)

Level I: based on Level A evidence or unanimous consensus of experts
Level II: based on Level B evidence and expert consensus
Level III: based on Level C evidence and expert consensus
Level IV: based on Level D evidence and expert consensus.

2 Evidence level of therapeutic measures

Level A: Data derived from meta-analysis or systematic review of multiple randomized clinical trials (RCT); multiple RCTs or a single high-quality RCT with adequate sample size.
Level B: Data derived from at least 1 relatively high-quality RCT.
Level C: Data derived from well-designed controlled trial without randomization, or well-designed cohort study or case–control study
Level D: Data derived from case series analysis without concurrent control or from experts' opinion.

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