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The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischaemic stroke

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ABSTRACT

The most effective medical treatment for acute ischaemic stroke (AIS) is to offer intravenous thrombolysis during the ultra-early period of time after the onset. Even based on the Consensus of Chinese Experts on Intravenous Thrombolysis for AIS in 2012 and 2014 Chinese Guidelines on the Diagnosis and Treatment of AIS, the rate of thrombolysis for AIS in China remained around 2.4%, and the rate of intravenous tissue plasminogen activator usage was only about 1.6% in real world. The indication of thrombolysis for AIS has been expanded, and contraindications have been reduced with recently published studies. In order to facilitate the standardisation of treating AIS, improve the rate of thrombolysis and benefit patients who had a stroke, Chinese Stroke Association has organised and developed this scientific statement.

BACKGROUND

The most effective medical treatment for acute ischaemic stroke (AIS) is to offer intravenous thrombolysis during the ultra-early period of time after the onset (within 4.5 hours). Recombinant tissue plasminogen activator (tPA), as the primary thrombolytic agent, has been proven effective and beneficial in patients with AIS and recommended by many guidelines worldwide. The 2012 edition of Consensus of Chinese Experts on Intravenous Thrombolysis for AIS (*Chinese Journal of Internal Medicine*) and 2014 Chinese Guideline on the Diagnosis and Treatment of AIS (*Chinese Journal of Neurology*) have greatly standardised stroke therapy in China.[1 2] However, the rate of thrombolysis for AIS in China remained around 2.4%, and the rate of intravenous tPA usage was only about 1.6%.[3] In 2015, American Heart Association (AHA)/American Stroke Association (ASA) published its Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke.[4] The indication of thrombolysis for AIS has been expanded, and contraindications have been reduced. In order to facilitate the standardisation of treating AIS, improve the rate of thrombolysis and benefit patients who had a stroke, Chinese Stroke Association (CSA) has organised and developed this scientific statement.

THE EVIDENCE OF INTRAVENOUS THROMBOLYSIS FOR PATIENTS WITH AIS

Time window and tissue window

AIS with the onset time within 4.5 hours

In 1995, National Institute of Neurological and Stroke Study (National Institute of Neurological Disorders and Stroke (NINDS)) demonstrated that intravenous tPA was safe and effective in treating AIS within 3 hours of onset.[5] It was the first time that intravenous tPA significantly improved the rate of survival and reduced disability. The sooner the treatment was provided, the better the outcome.[6–8] This treatment paradigm was supported by the European Thrombolysis Registry and Chinese Thrombolysis Registry.[7 9 10] In 2008, European Cooperative Acute Stroke Study III (ECASS 3) showed that intravenous tPA significantly improved the rate of 90-day favourable outcome (modified Rankin Scale (mRS) 0 or 1) in a selective group of patients with AIS within 3–4.5 hours of onset. This group was younger than 80 years old, without a history of diabetes or stroke and on any anticoagulant agents. ECASS 3 extended the treatment time window to 4.5 hours[11]. Subsequently, thrombolytic registries from China and other countries and a meta-analysis of intravenous thrombolysis provided further evidence to support the use of intravenous tPA within 3–4.5 hours.[8–10 12] Currently, all international guidelines unanimously agreed that intravenous tPA to treat patients with AIS within 4.5 hours of onset was safe and effective according to those published studies (table 1).

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Table 1 Intravenous tPA trials for acute ischaemic stroke as listed by the year of publication

Year	RCT study	Time window	Group	Conclusion
1995	NINDS[5]	0–3 hours	Placebo versus IV tPA 0.9 mg/kg	Improvement of the clinical outcomes at 3 months
	ECASS[32]	0–3 hours	Placebo versus IV tPA 1.1 mg/kg	Improvement of the 90 days' outcome with increased risk of haemorrhage in particular subgroup
1998	ECASS 2[140]	0–6 hours	Placebo versus IV tPA 0.9 mg/kg	No improvement of the 90-day clinical outcomes
1999	ATLANTIS B[141]	3–5 hours	Placebo versus IV tPA 0.9 mg/kg	No improvement of the 90-day outcome with increased risk of haemorrhage
2000	ATLANTIS A[142]	0–6 hours	Placebo versus IV tPA 0.9 mg/kg	No improvement of the 90-day clinical outcomes with increased haemorrhage and mortality risk
2008	ECASS 3[143]	3–4.5 hours	Placebo versus IV tPA 0.9 mg/kg	Improvement of the 90-day outcome with increased risk of haemorrhage
2016	ENCHANTED[144]	0–4.5 hours	IV tPA 0.6 mg/kg versus 0.9 mg/kg	The incidence of disability did not achieve non-superiority versus standard dose. Less safety concerns

All trials used mRS 0–1 as their efficacy outcome measure.
ATLANTIS, Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke; ECASS, European Cooperative Acute Stroke Study; ENCHANTED, Enhanced Control of Hypertension and Thrombolysis Stroke Study; IV, intravenous; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disorders and Stroke; tPA, tissue plasminogen activator.

Multimodal imaging-guided intravenous tPA therapy within 4.5–6 hours

A 2010 pool analysis showed that the risk would outweigh benefit if intravenous tPA was given beyond 4.5 hours[12]. Using multimodal neuroimaging study to expand the treatment window remained controversial.[13–17] By using MRI to look for mismatch of the ischaemic area between the perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI), the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) treated patients with AIS within 3–6 hours of onset.[14] In this trial, there was no significant difference in primary outcome between the intravenous tPA and placebo group.[14] However, cerebral reperfusion was improved, and infarct volume reduced in the patients who received intravenous tPA, with favourable outcomes on secondary outcome analysis.[18] Comparing with the control group, those who received intravenous tPA within 3–6 hours based on the findings of multimodal imaging mismatch had more favourable outcome.[8] Patients treated in the expanded time window had a similar rate of intracranial haemorrhage compared with those in the control group.[15]

The comparison of the data of five prospective European stroke registries showed similar efficacy and safety among patients treated within 3 hours, who had only a routine CT scan.[17] In another prospective comparative study, the rate of symptomatic intracranial haemorrhage (sICH) was not related to the outcomes between patients selected by multimodal imaging but beyond time window and those treated within 4.5 hours had only a routine CT.[15] Multimodal-guided thrombolysis could potentially expand the intravenous treatment time window to 4.5–6 hours, though more research is necessary. The ongoing ExTEND (ECASS 4) trial and reanalysis of the International Stroke Trial (IST)-3 perhaps could provide new evidence.[19–22]

The time window of using intravenous tPA to treat patients with posterior circulation ischaemic infarctions

About 20% of ischaemic stroke was in the posterior circulation.[23 24] Whether the basilar artery was able to be recanalised by intravenous tPA or not could be related to the length of the thrombus.[25] The reperfusion rate was about 20%–30% if the length of thrombus was >30 mm[26]. The large multicentre observational Basilar Artery International Cooperation Study Registry (BASICS) included patients with acute basilar artery occlusion and treated with thrombolysis up to 9 hours[27]. Intravenous thrombolytic therapy and endovascular therapy have both demonstrated improved outcome, especially in patients with severe strokes.[27–29] The patients with basilar artery occlusion might have an extended time window but still requires large clinical trials to confirm.

Stroke with unknown onset of time or stroke on awakening

About 20%–25% of stroke happened during sleep so the onset time was often unclear.[30] A retrospective study showed that in patients with AIS on awakening, selective thrombolysis (intravenous or intra-arterial thrombolysis) under the guidance of CT or MRI perfusion study had favourable clinical outcome but with increased mortality rate.[31] Since changes on the other standard MRI sequences (ie, increased T2 signal within affected tissues, best seen on FLAIR) occur later with the development of parenchymal oedema, this time difference between DWI and other MRI sequences has been used to estimate the time of stroke onset by assessing for a

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Table 2 List of other intravenous thrombolytic drugs

Agent	Mechanism	Trial	Implication	Results
Urokinase (UK)	Directly act on fibrinogen	UK[37]	UK 1.5 million IU group (n=155), UK 1 million IU group (n=162, placebo group (n=148)	Thrombolysis was safe and effective
Tenecteplase	More specific binding of fibrinogen to plasminogen into plasmin	ATTEST[145]	Tenecteplase and tPA group (n=52, respectively)	Onset within 4.5 hour in patients with AIS treated with tenecteplase and alteplase had similar neurological and imaging outcome
		TEMPO-1[146]	Tenecteplase (0.1 mg/kg and 0.25 mg/kg group (n=25 respectively)	Onset within 12 hours in patients with mild AIS (NIHSS ≤5 min) with intracranial artery occlusion. Better outcome in 0.25 mg/kg group.
Desmoteplase	Very strong fibrinolytic activity	DIAS-3[147]	Desmoteplase group (n=247), placebo group (n=245)	Onset within 3–9 hours in patients with AIS with cerebral artery occlusion or high-grade stenosis No better outcome in desmoteplase group but less safety issue.

ATTEST, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; DIAS, Desmoteplase in Acute Ischemic Stroke; NIHSS, National Institution of Health Stroke Scale; TEMPO, TNK–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke with Proven Occlusion; UK, urokinase.

DWI–FLAIR mismatch. Although DWI changes can be identified within minutes of stroke onset, FLAIR changes may not be apparent until several hours later. Patients with large areas of mismatch are therefore deemed to have had likely a more recent onset time of stroke and could potentially be eligible for intravenous thrombolysis even if an absolute stroke onset time is not available. The signal intensity ratio of DWI/PWI mismatch of <1.15 would indicate that the time of onset was within 4.5 hours[16]. In MR WITNESS Study, intravenous tPA is safe and feasible in selected subjects treated within 4.5 hours after symptoms discovery, with a median time to intravenous tPA of >11 hours since last time known well. However, asymptomatic ICH was often but not significant. Currently, the intravenous tPA for patients with wake-up stroke or stroke of unclear onset time is still being explored.[21 22]

Dosages of intravenous tPA

ECASS-I used intravenous tPA at the 1.1 mg/kg[32]. Most of other studies used the dosage of 0.9 mg/kg (maximum 90 mg, 10% intravenous bonus over 1 min, rest infused over an hour).[5–7 11] The Japan thrombolysis registration studies suggested that 0.6 mg/kg tPA for patients with AIS was safe and effective, but the treatment did not compare with placebo.[33 34] In 2011, one thrombolysis meta-analysis of data from Chinese, Korean Singaporean and Vietnamese showed that intravenous tPA 0.9 mg/kg was more effective than that of 0.6 mg/kg, and with similar risk of haemorrhage.[35] Recently, Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) found that patients in low-dose tPA (0.6 mg/kg) group failed to achieve the non-inferiority in primary outcome measurements (mortality or disability) when compared with those in standard dose group in 90 days.[36] However, patients received 0.6 mg/kg had significantly lower rate of sICH and mortality within 7 days of enrolment.[36] The mortality rate was similar among both groups in 90 days. Therefore, low-dose IV tPA had better safety profile with less sICH but increased disability as measured by mRS comparing with those who received standard dose.[36] Based on the findings from the ENCHANTED study, standard dose of tPA still should be the first option while low dose can be a choice in patients with higher risk of developing intracranial haemorrhage.

Other intravenous thrombolytic drugs

Urokinase (UK) is one of intravenous thrombolysis agents in clinical practice in rural area of China due to its low cost. Only one paper published in Chinese literature indicated its efficacy and safety.[37] The trial enrolled 511 patients within 6 hours of onset and were assigned into three groups. Among patients treated with UK, 44.91% received 1.5 million units and 45.10% received 1.0 million units had a favourable outcome. In patients who received placebo, only 31.88% had minimal or no disability at 3 months. sICH within 36 hours after the onset of stroke occurred in 4.52%, 3.09% and 2.03%, respectively. Further studies are still needed to explore this optional choice in China (table 2).

Early neurological deterioration (END) and combination with antiplatelet therapy

END due to sICH

END is defined as an increasing of >4 points of National Institution of Health Stroke Scale (NIHSS) score from the baseline after thrombolysis. About 4.5%–10% of patients with intravenous thrombolysis could have END and were associated with a poor prognosis.[38] The common causes

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of END included expansion of ischaemia volume, persistent occlusion of vessel or reocclusion, sICH, small vessel disease, malignant cerebral oedema, early recurrent stroke, epilepsy and so on.[39]

Intracranial haemorrhage could be asymptomatic or symptomatic.[40–42] sICH was one of the major causes of END. However, the definition of sICH could vary. Per NINDS criteria, sICH was defined by a CT or MR scan plus clinical neurological deterioration.[5] Per ECASS 3 criteria, sICH was defined by worsening of NIHSS score by ≥4 points or death at 36 hours combined with presence of haematoma on imaging study.[11] The rate of sICH increases with the expansion of the treatment window.[18 42–47] Although intravenous tPA increased the risk of serious haemorrhage, the overall mortality rate was not increased. On the contrary, it significantly reduced the rate of death and disability.[5 7 11 48 49]

Currently, there are five models to predict the risk of haemorrhage after intravenous tPA: the Haemorrhage after Thrombolysis (HAT) score[40]; the Multicenter Stroke Survey (MSS) score[41]; the Glucose Level on Presentation, Race (Asian), Age, Sex (Male), Systolic Blood Pressure and Severity of Stroke on Presentation (GRASPS) prediction model[42]; Safe Implementation of Treatments in Stroke (SITS) score[45] and Blood Sugar, Early Infarct Signs, (Hyper) Dense Cerebral Artery Sign, Age, NIHSS score (SEDAN).[50]The predictive value of these models still requires further validation. The use of these tools should not exclude qualified candidates from receiving thrombolysis.

Angio-oedema and its treatment

Angio-oedema is rare and happens in 1.3%–5.9% of patients after intravenous tPA.[51–54] About 0.3% to 0.8% require emergent intubation.[51] These patients first experienced hemi-tongue oedema that usually subside within 24 hours[54]. The predisposing risk factors included the combination use of ACE inhibitor or the stroke involved insular or frontal lobe.[54 55] Treatments included steroid and antihistamines agents.[54] For those with severe symptoms, tracheostomy, intubation and artificial ventilation might be required.[54]

Evidence of combination of antithrombotic therapy

The evidence for early antithrombotic therapy after thrombolysis is insufficient. Antiplatelet Therapy in Combination With Recombinant t-PA Thrombolysis in Ischaemic Stroke (ARTIS) trial did not show improved outcome but increased rate of sICH. This randomised controlled study enrolled patients who had aspirin 300 mg at 90 min post intravenous tPA.[56] Combined Approach to Lysis Utilising Eptifibatide and Recombinant Tissue-Type Plasminogen Activator in Acute Ischaemic Stroke-Full Dose Regimen Stroke (CLEAR-FDR) trial found that the combination of standard dose of intravenous tPA and eptifibatide (glycoprotein IIb/IIIa inhibitors) was safe and effective but requires further approval.[57]

Recommendation

- For AIS patients with onset time <3 hours, intravenous thrombolysis should be offered if there are no contraindications (Class I, Level of Evidence A). Intravenous alteplase within the 3–4.5 hour window is also recommended for those patients who are <80 years old, without a history of both diabetes and prior stroke, NIHSS <25, not taking any oral anticoagulants and without imaging evidence of ischaemic injury involving more than one-third of the MCA territory (Class I, Level of Evidence B).
- When considering intravenous tPA, the sooner the treatment, the greater the benefit and the less the risk (Class I, Level of Evidence A). The dosage of intravenous tPA is 0.9 mg/kg (maximum 90 mg), of which 10% is given as an intravenous bolus in 1 min, the remaining given as intravenous continuous infusion over 1 hour (Class I, Level of Evidence A).
- Lower dose of tPA (0.6 mg/kg, maximum 60 mg, of which 15% is given as an intravenous bolus in 1 min, the remaining given as intravenous continuous infusion over 1 hour) could be considered in AIS patients with high risk of developing haemorrhage (Class IIB, Level of Evidence C).
- If there is no tPA available or it is unaffordable, AIS patients within 6 hours of onset can be considered to receive IV UK. The dosage of UK is 100 million to 1.5 million IU, dissolved in 100–200 mL of saline and given as a continuous intravenous infusion over 30 min (Class IIb, Level of Evidence C).

USE OF INTRAVENOUS TPA IN PATIENTS WITH AIS WITHIN 3–4.5 HOURS AND OTHER SPECIAL CONDITIONS

Thrombolysis in the elderly

After age of 55 years, the risk of having AIS doubles for every additional 10 years of life.[58 59] AIS-related in-hospital mortality was 1–2 times higher in those ages older than 80 or 90 years according to the report from the Get with the Guidelines.[60 61] The risk of sICH also increased after intravenous tPA in AIS patients older than 80 years old.[39 62 63] However, a meta-analysis still revealed that intravenous tPA reduced 3-month mortality in patients >80 years.[62] The rate of sICH in older patients with AIS may vary by different criteria. When using the ECASS criteria, multiple observational studies found no increased risk of sICH in elderly patients post intravenous tPA.[64 65] However, the rate of sICH doubled in patients older than 80 years post intravenous tPA in NINDS trial.[62] A recent meta-analysis showed no significant difference post intravenous tPA comparing AIS patients ≥80 years with those <80 years.[63] Moreover, patients older than 80 in the ENCHANTED trial were safe in their subgroup analysis.[66]

Recommendation

- Older patients may have an overall poor prognosis post stroke with increased risk of mortality and haemorrhage comparing with younger patients. How-

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ever, older age does not change the potential benefit of thrombolytic treatment. In AIS patients who are >80 years and with onset time of <3 hours, intravenous tPA is recommended (Class I, Level of Evidence A). The benefit of full-dose intravenous tPA for AIS patients >80 years and within 3–4.5 hour of onset is unclear (Class IIb, Level of Evidence B).

The issue of stroke severity and stroke subtypes

Mild or severe stroke was removed from the list of exclusion criteria[67] in the 2013 AHA/ASA guidelines on the management of AIS. For those strokes that take place within 3–4.5 hours of onset, patients with severe stroke were still excluded.[67]However, the ENCHANTED trial has shown that it was safe for both mild and severe stroke patients in its subgroup analysis.[66]

Severe strokes

For severe stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset. However, it was one of the contraindications for the 3–4.5 hour time window in ECASS 3.[11] The severity of stroke at baseline is the strongest predictor of future functional independence or mortality in patients after their first AIS.[58 63] Subgroup analysis of NINDS studies found that patients with severe strokes could still benefit from IV with a favourable outcome comparing with those not treated.[68] Patients with severe strokes had a higher rate of haemorrhagic transformation and in these patients, haemorrhage might not be related to the use of intravenous tPA.[29] The evidence is insufficient to not offer intravenous tPA to patients with severe strokes or early signs of infarction. Patients with severe stroke and early ischaemic changes on CT was not a contraindication for intravenous tPA.[16 69 70]

Mild stroke

NINDS studies did not list the lower limit of the[71 72]NIHSS score for using intravenous tPA.[5] Several meta-analysis have found that patients with mild stroke were still significantly disabled at 3 months[71–76]. Such disability could be from motor deficits, cognitive impairment, fatigue or depression, which could not be assessed by NIHSS.[71 77 78] Since then, the ENCHANTED trial has also included patients with mild strokes between 3 and 4.5 hours of onset.[66] Although the trial did not reach its predetermined non-inferiority hypothesis, intravenous tPA 0.6 mg/kg showed some efficacy but less haemorrhage in this subgroup.[66] Rapid improvement and mild stroke were two main reasons of why thrombolysis was not given.[79] The treatment should not be delayed due to the improvement of symptoms, while the treatment time window missed. Thrombolytic therapy should be given as early as possible.

Recommendation

- For AIS patients with severe stroke symptoms, intravenous tPA is recommended within 3 hours of symptom onset. Although risk of haemorrhagic transformation may increase, there is still proven clinical benefit (Class I, Level of Evidence A). For patients with mild but disabling stroke, intravenous tPA is indicated within 3 hours of onset (Class I, Level of Evidence A).
- For patients with mild but non-disabling stroke within 3 hours of onset, intravenous tPA might be administrated (Class IIb, Level of Evidence C). For AIS patients with moderate or severe stroke however clinically improving but still have neurological deficit, intravenous tPA is recommended (Class IIa, Level of Evidence A).
- Onset to treatment time is a main factor predicting the outcome; therefore, continuing to observe patient and delay the treatment with intravenous tPA is not recommended (Class III, Level of Evidence C).
- Intravenous tPA treatment is indicated in patients with early ischaemic changes on CT stroke and within the tPA time treatment window (Class I, Level of Evidence A).
- Intravenous tPA is reasonable for patients with moderate to severe ischaemic stroke and early improvement but remain moderately impaired and potentially disabled (Class IIb, Level of Evidence C).
- Intravenous tPA is not recommended to patients with extensive hypodense lesion on CT scan. Extensive hypodense lesions may predict that the damage of brain is irreversible (Class III, Level of Evidence A).
- For patients with mild but disabling stroke symptoms, intravenous tPA is indicated within 4.5 hours of symptom onset (Class IIb, Level of Evidence A). Treatment of patients with mild ischaemic stroke symptoms that are judged as non-disabling may be considered, but the benefit is unclear.

Subtypes of stroke

The subgroup analysis of NINDS studies in 1995 has found that all subtypes of patients with AIS would benefit from intravenous tPA.[80] A multicentre registry study has found that a small number of patients with large vessel stenosis would have a better 7-day prognosis with thrombolysis.[81] However, all subtypes improved with no statistical significance by 90 days[81]. One study found that early intravenous tPA would benefit AIS patients with cardiogenic middle cerebral artery occlusion.[82] Another large study did not find any significant difference in treating patients with cardiogenic or non-cardiogenic type of stroke.[83] One Chinese prospective single-centre study suggested that mild cardiogenic stroke was a predictor of mortality[84]; another study revealed that patients with cardioembolic stroke had an increase risk of haemorrhage after thrombolysis but without statistical significance among all subgroups of patients with sICH.[85]

About a quarter of stroke was of lacunar type and usually had favourable outcome,[80] which was supported by two large national registry studies.[81 86] Lacunar stroke was also an independent prognostic factor for favourable outcome.[85 87] However, some still had concerns of the risk with thrombolysis in patients with small vessel disease or previous history of small cerebral vasculopathy.[70 88]

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Recommendation

- Intravenous tPA is indicated for patients with AIS of all subtypes. There is no need to delay the treatment in order to rule out a possible cardiac source of emboli, such as in patients with atrial fibrillation (Class II, Level of Evidence A).
- The benefit of intravenous tPA is unclear in AIS patients with small cerebral vasculopathy (Class III, Level of Evidence C).

Intravenous tPA in patients with previous use of antithrombotic agents

Patients who had a stroke are often on antithrombotic agents, oral anticoagulants, heparin or low molecular weight heparin (LMWH) and/or recent treated with of tPA. A small retrospective study explored the safety of thrombolysis in patients on antiplatelet agents and found that the risk of sICH was not increased, but parenchymal ICH rate rose substantially.[89] One retrospective study in China found potential risk of sICH in patients on antiplatelet therapy.[90] One large randomised controlled study reported that patients on antiplatelet agents had a trend of developing haemorrhage but without statistical significance,[7] which was supported by meta-analysis findings.[91]

According to the previously published guidelines and drug information, INR >1.7 or PT >15 s in AIS patients with onset of <3 hours were two contraindications for intravenous tPA.[1 67] In addition, regardless of the value of INR, it would be contraindicated if a patient was on anticoagulant.[11] One large registry study demonstrated that warfarin increased the risk of sICH.[92] However, after adjustment for stroke severity, age and comorbidities, the risk of sICH was not increased if INR was in the therapeutic range.[46] Compared with unfractionated heparin, LMWH does not prolong PTT but has more biological activity and longer duration of action. Therefore, patients on LMWH within 24 hours of onset of stroke are not suitable for intravenous thrombolytic therapy due to increased risk of haemorrhage.

Direct thrombin inhibitors (dabigatran and argatroban) have become the first-line treatment for stroke prevention in patients with non-valvular atrial fibrillation or peripheral vascular disease. A prospective study of 65 patients who received combination of intravenous argatroban and tPA found that the rate of recanalisation rate was 61% and rate of haemorrhage was 4.6%.[93] Idarizumab, as the antidote of dabigatran, can block the action of dabigatran in several minutes. After careful consideration and reversal of dabigatran with idarizumab, intravenous tPA could be given.[94] PT and aPTT could be prolonged in patients on oral FXa inhibitors (apixaban and rivaroxaban). Even with normal aPTT, INR, platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assays, or no history of receiving these non-vitamin K oral anticoagulants in the past 48 hours (assuming renal function is normal), the efficacy and safety of intravenous tPA remains unclear.

Recommendation

- Intravenous tPA is indicated in patients who are on aspirin, clopidogrel, dual antiplatelet therapy or warfarin with an INR ≤1.7 (Class IIb, Level of Evidence B).
- Intravenous tPA is contraindicated in patients on warfarin with an INR >1.7 (Class III, Level of Evidence B).
- Intravenous tPA is contraindicated in patients on LMWH within the previous 24 hours, no matter LMWH is used for prevention or treatment of thrombosis (Class III, Level of Evidence B). If the patient has not received a dose of these for >48 hours, intravenous tPA should be considered.
- The evidence of giving intravenous tPA in patients on either direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but could be harmful (Class III, Level of Evidence C).
- The use of intravenous tPA in patients on direct thrombin inhibitors or direct factor Xa inhibitors is not recommended (Class III, Level of Evidence C).

Platelet count

Although platelet count of <100 000 mm^3 was a contraindication for thrombolysis, clinically patients with thrombocytopaenia were rare and a large pooled analysis reported that it was present in only small number of cases.[95] Another two observational studies confirmed this finding and reported that the rate of sICH was low.[96 97]

In the past, test of clotting function was essential before thrombolysis. Clinical research found that INR was rarely elevated in patients not on any anticoagulants, or in hepatic failure, sepsis or other non-drug-related coagulopathy condition. One large registry study reported that 7 out of 152 patients with INR >1.7 or PT >15 s had sICH.[96] After adjustment for age and baseline NIHSS, the prognosis of patients with INR >1.7 was not worse than others. Therefore, the safety or efficacy of intravenous tPA in patients with INR >1.7, aPTT >40 s, or PT >15 s cannot be confirmed currently. Since the chance of discovering thrombocytopaenia is rare in patients with AIS, unless there is a history of coagulopathy, it is unnecessary to check for coagulation studies prior to starting thrombolysis.

Recommendation

- Intravenous tPA is not recommended in AIS patients with platelet count of <100 000/mm^3, INR >1.7, aPTT >40 s or PT >15 s (Class III, Level of Evidence C).
- Given the low risk of having thrombocytopaenia or coagulopathy in general population, there is no need to wait for the results of coagulation studies before considering intravenous tPA unless patient has history of coagulopathy (Class IIa, Level of Evidence B).
- Intravenous tPA may be considered in patients with ESRD and on haemodialysis and other potential bleeding disorder if their coagulation studies are normal (Class IIb, Level of Evidence C).
- Other stroke mimic conditions.

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Issue of abnormal glucose level

Hypoglycaemia and hyperglycaemia are known to produce acute focal neurological deficits. China National Stroke Registry has found that <1% had a stroke mimic condition. In AIS patients with blood glucose levels of <50 mg/dL or >400 mg/dL, neurological examination should be repeated once abnormal glucose levels are corrected. If stroke symptoms still exist, intravenous tPA should be considered.

Recommendation

- Intravenous tPA is recommended in otherwise eligible patients with an initial glucose levels of >50 mg/dL (Class I, Level of Evidence A).
- If baseline blood glucose level is >400 mg/dL in patients with AIS, hyperglycaemia should be corrected first and then if neurological deficits are still present, intravenous tPA should be considered (Class IIb, Level of Evidence C).

Seizure at stroke onset

In the literature, over 300 patients with seizures at onset of stroke were treated with intravenous tPA.[13 53 54 74 98] Among them, two had sICH. One of these patients had a remote history of surgical removal of a brain tumour. Therefore, seizure at onset of stroke is not an absolute contraindication for intravenous tPA.

Recommendation

- Intravenous tPA is reasonable in patients with a seizure at the onset of acute stroke, and the limb impairment is 'thought' to be from stroke and not from Todd's paralysis (Class IIa, Level of Evidence C).

Hypertension crisis

Patients with hypertension crisis may mimic stroke or top of the basilar artery occlusive syndrome. Uncontrolled or severe hypertension (systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg on two or more consecutive measurements) is a known risk factor for postintravenous tPA sICH.[44] Therefore, intravenous tPA is contraindicated unless the very elevated blood pressure is emergently controlled.[99]Two national stroke registries have found that the higher the blood pressure post intravenous tPA, the higher the risk of developing sICH.[45 81] In the ENCHANTED trial, patients were randomised to the group with tight blood pressure control or standard blood pressure control.[66] The trial found that patient had no better outcome if blood pressure was low. Presently, there is no strong evidence to support strict control of blood pressure prior to intravenous tPA aside from the recommended treatment range of <185/110 on administration and <180/105 thereafter.[100]

Recommendation

- Intravenous tPA is indicated after treatment of hypertension to the goal of <185/110 mm Hg. Clinicians should stabilise blood pressure before starting intravenous tPA (Class I, Level of Evidence B).
- Clinicians should lower blood pressure to the goal of <180/105 mm Hg after intravenous tPA has been given and maintained blood pressure at this level for at least 24 hours (Class I , Level of Evidence B).

Conditions that may potentiate haemorrhage disease

Tendency to develop haemorrhage in potentiate haemorrhagic diseases

Conditions that may potentiate haemorrhage include liver cirrhosis, end stage renal disease, haematological malignancy, vitamin K deficiency, sepsis, antiphospholipid antibody syndrome or potential bleeding disorder. The safety and efficacy of intravenous tPA in these patients are unclear.

Intravenous tPA in pregnancy and peripartum period

Currently, there is no evidence on whether pregnant woman can have intravenous tPA. It may be considered if not teratogenic. Only one review identified 12 reported cases of pregnant women with AIS received either intravenous tPA or endovascular therapy.[95]

Recommendation

- In patients with history of potential haemorrhage diathesis or coagulopathy, the efficacy and safety of IV tPA are unknown. In these patients, intravenous tPA should be considered on an individual basis (Class IIb, Level of Evidence C).

Recent history of trauma, surgery or biopsy

A few studies considered that major surgeries should be the absolute contraindications for intravenous tPA. Clinicians must thoroughly balance the benefit of intravenous tPA and risk of haemorrhage with recent surgery. If the haemorrhage of a surgical site is compressible, thrombolysis can be given in selected patients. There is currently limited data on the use of intravenous tPA in patients with trauma. One report of 121 patients with dissections and treated with intravenous tPA showed no safety concerns when stroke their AIS was from the dissection of the cervical vessels related to trauma.[101]

Major intracranial/spinal surgeries might increase the risk of haemorrhage at the site of operation after intravenous tPA and therefore negate any benefit of thrombolysis. Previously, intravenous tPA was contraindicated in patients with AIS who had non-compressible arterial puncture site within 7 days of onset of stroke.[67] With the advent of bridging therapy, patients now are receiving both intravenous and IA therapy despite the puncture of the femoral artery after intravenous tPA.[102–109] Therefore, groin puncture itself is not a contraindication for intravenous tPA anymore.

Recommendation

- For patients with major head trauma or a history of intracranial/spinal surgery within the prior 3 months, intravenous tPA is potentially contraindicated (Class III, Level of Evidence C).

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- The safety and efficacy of administering intravenous tPA to patients with AIS who have had an arterial puncture of a non-compressible site within 7 days is uncertain (Class IIb, Level of Evidence C).
- Intravenous tPA therapy should be avoided in patients who have had lumbar puncture within last 7 days, although it can still be considered (Class IIb, Level of Evidence C).

Previous intracranial abnormalities

Limited data are available in patients with history of stroke within 3 months and treated with intravenous tPA. Case series reports suggested that patients with a history of unruptured intracranial aneurysms were safe when treated with intravenous tPA and without significantly increased risk of haemorrhagic transformation.[110–115] Even these reports could be biased, evidence indicated that intravenous tPA in these patients was relatively safe. Safety of intravenous tPA in patients with intracranial vascular malformations (cavernous haemangioma, telangiectasia, developmental venous abnormality, arteriovenous malformations and arteriovenous fistula) is unclear.[116–118]

Recommendations

- Use of intravenous tPA in patients presenting with AIS and a prior history of ischaemic stroke <3 months may be harmful (Class IIb, Level of Evidence B).
- For AIS patients with a small or moderate sized (<10 mm) unruptured intracranial aneurysm, intravenous tPA is reasonable (Class IIb, Level of Evidence C).
- In AIS patients with a giant unruptured intracranial aneurysm, the balance of benefit and risk is unclear (Class IIb, Level of Evidence C).

Haemorrhagic retinopathy or other haemorrhagic ophthalmological conditions

The condition of having an ischaemic stroke and intraocular haemorrhage is rare. In patients without diabetes, the rate of developing retinal haemorrhage after intravenous tPA was around 0.003%.[119] Such haemorrhage is also rare in patients with diabetes . Therefore, intravenous tPA is not contraindicated in patients with diabetic retinopathy.

Recommendation

- Intravenous tPA is indicated in patients with diabetes with haemorrhagic retinopathy or other history of intraocular haemorrhage. However, the risk of developing blindness from haemorrhage is real. The balance of benefit and risk of intravenous tPA should be discussed before treatment (Class IIa, Level of Evidence B).

Concomitant heart disease

AIS patient with concomitant myocardial infarction (MI) should receive intravenous tPA at 0.9 mg/kg first and proceed to percutaneous transluminal coronary angioplasty and stenting therapy (PTCAS). In these patients, pretreatment with intravenous tPA does not decrease the benefit of coronary PTCAS. There is limited data on the benefit of intravenous tPA in patients with recent MI (3 months). The benefit may vary depending on the type of MI the patient has (ST segment elevated MI, STEMI vs non-STEMI) and the location of MI.

Recommendation

- For AIS patients with history within the past 3 months, also presenting with concurrent non-STEMI (Class IIa, Level of Evidence C), right cardiac wall or inferior wall MI (Class IIa, Level of evidence C) and recent STEMI of left anterior wall MI (Class IIa, Level of Evidence C), intravenous tPA is indicated.

NEW PARADIGM ON AIS AND INTRAVENOUS THROMBOLYSIS AND THE ESTABLISHMENT OF TREATMENT PROTOCOLS

Conducting public education and prehospital emergency response system

Only 24%–54% of AIS patients presented to the hospital within an hour of onset. Among them, 38%–65% came by emergency medical services (EMS).[120] Public stroke education may raise stroke awareness and improve stroke symptom recognition and shorten the onset to hospital arrival time and increase the rate of thrombolysis.[121]

The recognition of stroke by EMS staff was around 30%–83%. Ongoing EMS education on stroke recognition may help prioritise transportation and make prenotification to the emergency room and stroke team at the designated stroke centres, hence improve the rate of thrombolysis.[122] The AHA/ASA guidelines recommend that EMS personnel use one of the simple stroke screening tools to recognise stroke: Cincinnati Prehospital Stroke Scale, Los Angeles Prehospital Stroke Scale or the Face Arm Speech Time Tool (FAST tool).[67 105] Modelling, coding and quality improvement measures could help improve the sensitivity and specificity of their ability to recognise stroke.[123–126] Recently, the development of Stroke Recognition 120, a tool specifically designed to coincide with the Chinese emergency notification number, is being promoted by the C and its Red Ribbon Movement.[127] Since FAST is a good acronym for English-speaking population to recognise stroke signs and symptoms, Stroke 120 is a Chinese way of recognising 'Face, Arm and Speech' abnormality in stroke. Stroke 120 designates '1 as looking at One face for any asymmetry, 2 as looking for Two arms for any weakness and 0 as Listening for any speech abnormality'. Its usefulness is currently being studied.

Optimising stroke treatment in the emergency room

Optimising the process for intravenous thrombolysis will benefit more stroke patients, open more vessels, minimise disability and improve outcome. The benefit of intravenous tPA is significant when given within 3 hours, moderate within 3–4.5 hours and unclear beyond 4.5 hours.[8 63] The guidelines require that the time of

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initiating intravenous tPA on arrival be within 60 min (door to needle time, DTN).[67] In China, one of the main delays was the period between completing a brain scan and treatment, mainly from the consenting process.[128]

Through process improvement, the rate of DTN of <60 min was improved from 29.6% to 53.3%, and rate of mortality and haemorrhage was lowered in the USA.[129] Helsinki stroke model gave an example of requiring the emergency medical services to provide prenotification to emergency before patient's arrival.[123] EMS staff sent patient directly from the ambulance to the CT scan, and physician in emergency room were ready to administer intravenous tPA in CT scanner right after the CT was completed and showed no contraindications.[126] Their DTN has been shortened to less than 20 min.[130]

Consent

A written consent is needed before treatment according to the Chinese medical regulation, even the indication of intravenous tPA within 3 hours in AIS is an approved therapy. On average, it takes about 10 to 15 min to explain to the patients and relatives about the stroke and ask them to sign the consent.

Process for bridging therapy and standardisation of system of transfer for endovascular therapy

Despite the effectiveness of intravenous thrombolysis, intravenous tPA could only open about 17%–38% of large vessel occlusive strokes. The benefit was modest.[82 131] Patient's prognosis was directly related to the ability to re-establish the cerebral blood flow. The earlier the vessel opens up, the better the prognosis.[132] The key therefore is to improve the rate of recanalisation of the occluded vessels.

Between 2015 and 2016, seven published randomised controlled trials have confirmed that the combination of intravenous tPA with endovascular thrombectomy was safe and effective.[103 104 107 133–136] For those patients with large vessel occlusive type of AIS (only 15%–20% of AIS), bridging intravenous with IA therapy was better than intravenous thrombolysis alone.[39 109 132 137] Hence, the interventional treatment guidelines from both USA and China have recommended the bridging therapy for those AIS with anterior circulation large vessel occlusive AIS.[105 138]

For those with posterior circulation large vessel occlusive stroke, the large multicentre BASICS showed no improved outcome with either the combination or standard intravenous therapy only.[27] However, the Dutch National Registry Study showed that bridging therapy had equivalent of outcome for those with posterior circulation large vessel stroke compared with those in the Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) trial.[139]

It is proven that combined intravenous and IA endovascular therapy may improve the outcome in AIS patients with large vessel occlusive strokes only.[109] Therefore, stroke system of care and stroke care policy should be adjusted accordingly. Telestroke is one of the efficient method for comprehensive stroke centre to screen for a potential thrombolysis candidate and further transfer these patients from a primary centre or comprehensive stroke centre. Patients post intravenous tPA should immediately have the imaging study to check for any large vessel occlusion. If such occlusion is found, the patient should be taken to the stroke centre that can offer IA thrombectomy. A database should be established to track and evaluate the quality measures and clinical outcome at these stroke centres.[60 129] China is actively establishing stroke centres and exploring different stroke system of care models.

Recommendation

1. Improve public education and awareness of signs and symptoms of stroke, facilitate early transportation by ambulance and minimise delay of treatment (Class I, Level of Evidence B).
2. Recommend education and certification of qualified EMS personnel on the recognition of stroke signs and symptoms, establish priority transfer of stroke patients to a stroke centre that has established care protocol and can offer intravenous tPA. Provide EMS personnel with training on stroke screening tools (the FAST/LAPSS/the CPSS/Stroke 120), shorten any prehospital delay (Class I, Level of Evidence B; Stroke 120: Class IIb, Level of Evidence C).
3. Try to obtain a written consent as soon as possible (Class II, Level of Evidence C). If consent cannot be obtained from the patient, it can be obtained from patient's next of kin and/or legal representative before the treatment.
4. Support the establishment of a stroke unit, mobile stroke unit or telestroke service. (Class I, Level of Evidence B).
5. Optimising stroke triage in ER and shorten the delay. Recommend clinical quality improvement process by using these key performance indicators: door to CT time, DTN, door to puncture time and door to reperfusion time. (Class I, Level of Evidence B).
6. At stroke centres with ample resources, thrombolysis should be given in a room with monitors. Recommend performing laboratory tests, imaging studies and signing of consent simultaneously so to avoid the delay of treatment (Class IIb, Level of Evidence B).
7. Emergent stroke care can be completed at a primary stroke centre that offers intravenous tPA. Initial non-invasive vascular imaging should be completed quickly. Select those AIS patients eligible for endovascular therapy and transfer them to the nearest comprehensive stroke centre as soon as possible (Class IIb, Level of Evidence B).
8. Endovascular treatment should be performed in experienced stroke centres that can complete neurovascular imaging studies quickly and by experienced and certified interventional physicians. Conduct quality measures on the diagnostic and treatment process and patients treated should be followed up (Class I, Level of Evidence C).

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