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Comprehensive Management of Ischemic Stroke Based on the Concept of Ischemic Penumbra

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Abstract

Stroke is a cause of mortality and morbidity of immense magnitude, rating second only to cancer in the developing world. Humungous advances in the understanding of the pathophysiology and subtypes have resulted in paradigm shifts in approach to management. With the burgeoning stroke burden on the society it is imperative to keep pace with these advances. Treating strokes based on the concept of identifying and quantifying the critically perfused brain tissue called the "ischemic penumbra" by a rapidly available radiological marker have led to radical changes in the attitude amongst clinicians from being nihilistic to being aggressive and optimistic. The paper delineates these emerging concepts and summarizes the limited experience with the hyperacute thrombolysis of acute ischemic stroke patients in Indian setting.

Introduction

Years of nihilism later, acute stroke therapy has finally emerged, including thrombolysis with tissue plasminogen activator (rt-PA). However, rt-PA is limited by a narrow therapeutic time window period and side effects, so that only 5% of all stroke patients receive

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thrombolysis. Unimodal targeting of key events in stroke pathophysiology has not been effective in providing long-term benefits, leading to negative results in previous clinical neuro-protective stroke trials. A successful future stroke therapy needs to approach multiple pathophysiological mechanisms besides revascularization/ reperfusion including thrombolytics, related adverse side-effects, prevention of apoptosis (programmed cell death), stimulation of neuro-regeneration and neuronal plasticity.

Thrombolytic therapy is an inherently attractive treatment for acute ischemic stroke (AIS), based on the known pathologic and angiographic substrates of ischemic cerebrovascular disease. Most ischemic strokes are the direct consequence of atherothrombosis or a thromboembolism of a cerebral or pre-cerebral artery. The critical event is usually the formation of an acute thrombus. The basis for thrombolytic treatment is to achieve rapid arterial recanalization with a relatively safe agent, soon enough to improve patient outcome. Reperfusion is the most beneficial of all therapeutic strategies for acute ischemic stroke. There is Level I evidence now which shows that thrombolysis in cases of AIS is effective if administered with in 3 hours of stroke onset. This benefit has been shown to be time dependent and potentially extends beyond 3 hours, with evidence that potentially viable penumbral tissue may be present in a significant proportion of cases well-beyond 3 to 6 hours and in isolated cases, up to 48 hours.

The standard cerebral reperfusion treatment of the first decade of the reperfusion era, non-contrast CT guided = 3 hours intra-venous tissue plasminogen activator, has many limitations. This review surveys emerging strategies that have the potential to extend cerebral reperfusion therapy beyond 3 hours time window as well as the means to bridge the "stroke recovery gap" (defined as the difference observed between the clinical response to thrombolytic therapy in a given population of patients presenting with ischemic stroke and the potential clinical recovery if all of the penumbra were salvaged under ideal circumstances). Approaches to this include: 1). Intra-arterial pharmacological reperfusion approaches, combined intravenous-intra-arterial fibrinolysis and combined fibrinolytics and GPIIb-IIIa agents, 2). Emerging endovascular mechanical reperfusion strategies including intra-arterial thrombectomy (clot retrieval devices and suction

thrombectomy devices), mechanical disruption (micro-guide wire passage, laser photo acoustic emulsification, primary intracranial angioplasty), 3). Augmented fibrinolysis by endovascular ultrasound, 4). Multimodal imaging with magnetic resonance (MRI) or CT to rapidly assess the infarct core, penumbra, site of vessel occlusion and tissue hemorrhagic propensity, enabling improved selection of patients for reperfusion therapy beyond any arbitrary fixed time window, 5). Newer thrombolytic agents and 6). Adjunctive therapies such as neuroprotectants.

Intra-venous Thrombolysis in AIS

The National Institute of Neurological Disorders and Stroke (NINDS) study on the intravenous use of recombinant tissue plasminogen activator (rtPA) within 3 hours of a an acute ischemic stroke has shown the benefit of this form of treatment . In order to be effective the protocol for institution of rtPA therapy must be strictly followed. The evidence for this form of therapy is of level I. When all accumulated evidence for rtPA therapy is considered, the relative risk reduction provided by it is 44%, absolute risk reduction is 13% and the number needed to treat to save one person from death or disability is 7.

Many countries now routinely thrombolyze all patients of acute ischemic stroke who resent within the 3-hour time window and do not have any contra-indication. However, many stroke units, especially those in the developing nations, are hampered by constraints of resources and lack of awareness. Feasibility of thrombolysis is still being evaluated at these centers. The hyperacute thrombolysis for stroke was started in the year 1995-1996 in India and in March 2002 at All India Institute of Medical Sciences, a tertiary referral center in India. We assessed the outcome of patients treated with intravenous rtPA, including the incidence of intracerebral hemorrhage and other adverse events.

AIIMS is a large tertiary referral center in North India catering to almost 14 million people in Delhi. An earlier study found nearly 10-15% of patients with acute stroke to present within 3 hours to the Emergency services (unpublished). Since the catchment area is large and the population served is more than 14 million, this 10% could translate to significant numbers. Nearly 350-400 cases of acute stroke are seen every year at AIIMS.

The variables that were specifically recorded for each patient treated with rtPA: time of symptom onset, time of

arrival in the emergency department, time of CT scan examination and the time of rtPA administration. An extensive neurological examination including the baseline NIH Stroke scale (NIHSS) was performed in all patients. Other parameters noted were the demographic profile, stroke risk factors, baseline CT scan findings and the blood pressure measurements.

Potential benefits and significant risks, specifically the four fold greater risk of symptomatic intra-cerebral hemorrhage after thrombolytic treatment were discussed with all patients and /or their families and informed consent obtained. The tPA protocol was based on protocols published by the American Heart Association and the American Academy of Neurology. Inclusion and exclusion criteria are shown in Table 1.

All patients had pretreatment CT scans that were read by the attending neurologist together with the radiologist. Each of our patients received 0.9 mg/kg of intravenous rtPA upto a maximum of 90 mg, based on the estimated or actual body weight. Ten percent of this calculated dose was injected as a bolus and the remainder infused over an hour. Heparin and aspirin were withheld for the first 24 hours after rtPA administration in all our patients. Hypertension was treated using intravenous labetolol, or intravenous enalapril. Occasionally injection nitroglycerine or nitroprusside was required.

Results of follow-up CT scans or MRI scans were recorded in all patients thrombolysed. The use of aspirin, clopidogrel, heparin, acitrom and antihypertensives during the hospital stay was noted. The peak blood pressure during rtPA administration as well as during the first 24 hours after the infusion was recorded (Stroke subtype was determined by using the following classification: 1). Large artery atherosclerosis, 2). Cardio-embolic, 3). Small-vessel occlusion, 4). Stroke of other determined etiology, 5). Stroke of undetermined etiology using the TOAST criteria. We obtained telephone or clinic follow-up with the patient and caregiver in all 54 cases and assessed the Barthel Activities of Daily Living Index. For analysis, we defined a good outcome as an improved NIHSS of = 4 and a Barthel Index of = 75%. At AIIMS, due to constraints of time and resources we deviated from the recommended NINDS protocol in excluding patients with a history of liver or renal disease and in not obtaining results of platelet counts, prothrombin time and activated partial thromboplastin time in patients prior to thrombolysis.

Table 1

Criteria for use of tissue plasminogen activator (rtPA) in treating acute ischemic stroke at All India Institute of Medical Sciences

Clinical Inclusion Criteria

- Patient/care giver able to give informed consent before study procedure.
- Age = 18 years.
- Onset of symptoms of ischemic stroke within 0-3 hours.
- Measurable neurological deficit defined as impairment of language, motor function, cognition, and/or gaze, vision or neglect.
- Score for stroke severity = 4 on the National Health Stroke Scale (NIHSS).

Clinical Exclusion Criteria

- Severe symptoms (coma or severe obtundation with fixed eye deviation and complete hemiplegia or NIHSS score > 22).
- Minor stroke symptoms (NIHSS score < 4) or those that are rapidly improving.
- History of stroke in previous 6 weeks.
- Seizure at onset unless the treating physician is convinced that the neurological deficit is due to stroke and not seizure.
- Previous known intracranial hemorrhage.
- Hemorrhage in pretreatment CT scan of the brain.
- Uncontrolled baseline hypertension (> 185/110 mm Hg).
- Myocardial infarction in past 30 days.
- Recent (< 15 days) surgery, major arterial puncture, trauma or ulcerative wounds.
- Known and clinical evidence of chronic or acute hepatic or renal disease.
- Known bleeding diathesis/ coagulopathies.
- Patients on anticoagulants.
- Pregnancy, lactation, or parturition within the previous 30 days.
- Hypoglycemia, hyperglycemia (baseline serum glucose level must be between 50 mg% - 400 mg%).

Computed Tomography Exclusion Criteria

- Evidence of acute or chronic intracranial bleeding on CT.
- Likely etiology other than acute brain ischemia.
- Early signs indicating infarct of more than a third of the territory of the middle cerebral artery.

Fifty four patients received IV rtPA for AIS between March 2002 and March 2006. The stroke team was notified of 1096 patients suspected of having an acute stroke during this period. The most common reasons for disqualification from thrombolytic therapy were, exceeding the window period (38%), intracerebral hemorrhage (20%), minor or rapidly resolving symptoms (20%), and a non-stroke diagnosis (12%). Of the patients who could qualify to received thrombolysis, 26% could not be thrombolyzed since they could not afford rtPA.

The mean age of our patients was 66 years, ranging from 32 to 82. The mean blood pressure at admission was 156/88 mmHg and the mean maximum pretreatment blood pressure was 166/90 mm Hg. The mean baseline NIHSS was 14± 2 (range 8-22). Using TOAST criteria, patients were classified into: large artery atherosclerotic = 13; cardioembolic = 12; small vessel occlusion = 22; other determined etiology = 3; undetermined etiology = 4. The mean time to reach emergency was 2.4 hours (1.15 - 3.4 hours). The mean door to CT time was 24 minutes (10 - 47minutes). The mean door to rtPA injection was 26.8 minutes (25 - 67 minutes). The NIHSS scores ranged from 11 to 22 minutes (mean = 15.5 ± 2.7). Patients with history of liver or renal disease or on anticoagulants were excluded. PT, aPTT and platelet count results were not obtained prior to thrombolysis. Early signs of infarction on CT were seen in 25/54 (46.3%) patients. These were sulcal effacement in 11, insular ribbon sign in 6, and loss of gray white matter definition in 8. An infarct in the follow-up CT or MRI was present in 53 of our 54 patients (97.1%).

Mean length of hospitalization in our patients was 9 days. Hemorrhagic conversion was noted in 5(8.8%). Symptomatic intracranial hemorrhage or fatal hemorrhage did not occur in any of our patients.

Thirty five patients (65%) significantly improved on NIHSS at 48 hours (= 4 points) (mean change = 10; range = 4-17). At one month, 43 (79%) improved on Barthel Index (mean change = 45%). Of these, 19 (44% of the 43 patients improved; 35% of total number[54]), achieved = 95% scores on Barthel Index indicating near normal functional status. Of the stroke subtypes, cardioembolic and small vessel occlusions did better than others. Of the 8 patients who showed no improvement, 6 were lacunar strokes. One developed small frontal lobe hemorrhage and recurrent stroke; one died of aspiration and 8 showed no

improvement. The mean length of follow up after discharge was 9.5 ± 3 months.

We succeeded in treating 54 patients of acute ischemic stroke with IV rtPA over a period of four years. Importantly, we were unable to thrombolyse 38% of otherwise eligible patients due to delay in evaluation and treatment. The stroke subtype by final diagnosis was most often, in 35.3% patients, small vessel disease. The NINDS trial and few subsequent studies have shown that intravenous thrombolysis within the 3 hour time window is similar between different stroke subtypes. Patients arrived in the emergency department an average of 150 minutes after the symptom onset. A CT scan was performed within 22 minutes and intravenous rtPA was administered within an average of 27 minutes from the time of arrival to the emergency department respectively. A significant difference between our experience and the NINDS trial is that half of the patients randomized in the NINDS study were treated within 90 minutes of stroke onset. However, the response to treatment observed in the NINDS trial between patients treated under 90 minutes and between 90 and 180 minutes did not differ. This underlines the importance of not withholding treatment from patients even if they present beyond 90 minutes of symptom onset. We were able to treat patients within an average of 27 minutes from their time of arrival at the emergency department. This is contrary to the popular perception that it is generally not possible to treat patients within the time window of 180 minutes in busy and constrained hospitals of developing countries unless they arrive early. Recent NIH consensus guidelines recommend a "door-to-needle" time of 60 minutes or less for acute stroke patients.

An improvement of 4 points or more on the NIHSS at 48 hours was seen in 65% of our patients while a Barthel Index of 75 or more at 1 month was present in 79% patients. It is important to note here that the long term benefit as observed from the Barthel Index is significantly more impressive than the immediate benefit as reflected from the 48 hour NIHSS. The reluctance of many neurologists to treat patients is based on this premise of insufficient immediate improvement in outcome. However, it is equally important not to lose sight of the delayed benefits, especially considering the tremendous impact that stroke morbidity has on the individual, caregivers, and society as a whole.

This preliminary data from a tertiary care center from a developing country shows that hyperacute thrombolysis in acute ischemic stroke is both feasible and useful. It also emphasizes the importance of increasing awareness about stroke and its acute management. More significantly, till such time that patients start presenting more promptly for treatment, it needs to be understood that thrombolysis can still be provided in hospitals if a dedicated stroke team endeavors to reduce the "door-to-needle" time to the minimum possible.

The limitation of the present study is the lack of a control group which will impede with the assessment of efficacy of thrombolysis. However, since the study is strictly observational, it may be taken as a pilot project to evaluate essentially the feasibility and safety.

Intra - arterial thrombolysis in AIS

Intra – arterial (IA) thrombolysis provides an alternative to intravenous thrombolysis in selected patients with AIS. Recent advances in the field of neuro interventional radiology, with the development of extremely soft, complaint microcatheters and steerable microguide wires, along with high resolution fluoroscopy and digital imaging, and nonionic contrast agents, have made it feasible and safe to access the major intracranial blood vessels around the Circle of Willis from a percutaneous transfemoral approach under local anaesthesia. IA thrombolysis has been used most successfully in patients with acute middle cerebral artery (MCA) occlusion. There is evidence that the treatment window for IA thrombolysis extends to at least 6 h from stroke onset in patients with MCA occlusion. Other potential candidates for IA thrombolysis include patients with extracranial carotid artery (ICA) occlusion, intracranial carotid artery "T" occlusion or basilar artery occlusion.

Two randomized trials (1, 2) comparing intraarterial recombinant pro – urokinase (r – proUK) plus intravenous heparin vs intravenous heparin have been conducted in patients with occlusion of the MCA (M_1 & M_2) of < 6 h duration. The prolyse in Acute Cerebral Thromboembolism (PROACT) I trial treated 40 patients with MCA occlusion, with either IA r – pro UK (n = 26) or placebo (n = 14). All patients received intravenous heparin. The protocol initially specified a heparin dose of a 100 IU/ kg bolus and 1,000 U/h for 4 h. After 16 patients were randomized, the heparin dose was reduced to a 2,000IU bolus and 500 IU/ h 4 – h infusion on recommendations of the safety committee. The study drug

was started on an average, 5.5 h after symptom onset. Recanalization rates were significantally higher with r – proUK (58%) than with placebo (14%; 2 – sided p = 0.017). There was nonsignificant difference in the rate of early symptomatic hemorrhagic transformation, which occurred in 15.4 % of the r – pro UK patients and 7.1 % of the placebo – treated patients (2p = 0.64).

Ninety – day mortality rates (4% in pro UK group vs 7 % in the control group) and good clinical outcomes (30.4 % vs 21.4 %) favored treatment with r – pro UK but did not reach statistical significance. Recanalization rates and the risk of brain hemorrhage were influenced by the dose of heparin.

PROACT – II study (2) was designed to further test the efficacy and safety of IA r – pro UK in patients with MCA occlusion of < 6 h duration. More than 12,000 patients were evaluated for inclusion in the trial and 474 patients underwent a screening conventional cerebral angiogram. A total of 180 patients had angiogram – confirmed MCA occlusions and were randomized to receive 9 mg of IA r – proUK plus heparin (n = 121) or heparin alone (n = 59). The heparin dose was the same in both groups (2,000 – U bolus and a 500 U/h infusion of heparin for 4h). A clinically and statistically significant benefit favored r – proUK in the primary outcome analysis, with 40% of treated patients recovering to a mRS of ≤ 2 compared with 25 % of control patients (absolute risk reduction, 15 %; p = 0.043; relative risk reduction, 60 %). Mortality was 25 % in the r – pro UK group and 27 % in controls. Symptomatic ICH occurred in 10 % of r – proUK group and 2 % in controls (p = 0.063). The recanalization rate (Thrombolysis in Myocardial Infarction 2 or 3) was 66% for r – proUK vs 18 % for controls (p< 0.001). Patients recruited to PROACT II had moderate - to – severe strokes with a median baseline NIHSS of 17. The median time to start of intra – arterial treatment was 5.3h. Benefits of r – proUK were greatest in patients with baseline NIHSS scores of 11 to 20.

R – proUK is not available for routine clinical use. Reports of IA thrombolysis using tPA or urokinase in selected patients have generally showed favorable results, or better than anticipated clinical outcomes, despite increases in the rate of symptomatic ICH (3 -14).

Treatment had been given beyond 3 h in most cases, and patients often had severe stroke syndromes due to large – vessel occlusions. Symptomatic

ICH was more frequent with IA thrombolysis (9.5 % vs 3 %, p = 0.046).

IA thrombolysis in Vertebro basilar Territory

The natural history of basilar artery occlusion is extremely poor with mortality ranging from 83 % to 91 % (15). Because of this poor natural history, IA thrombolysis has been preferred in patients with acute basilar artery occlusion. Basilar artery occlusions are usually owing to atherothrombosis. There is a high incidence of residual stenosis after basilar artery recanalization, which often requires adjuvant therapies including angioplasty, antithrombotic and antiplatelet agents and stenting. Good outcomes are strongly associated with recanalization after thrombolytic therapy. Hacke *et al* (16) described 65 consecutive patients with vertebro – basilar occlusions treated either with local IA urokinase (UK) or IA SK plus heparin (n = 43) or conventional antiplatelet/ anticoagulation therapy (n = 22). The recanalization rate among thrombolysis cases was 44% (19 of 43). All patients without recanalization died whereas 14 of 19 with recanalization survived, 10 with favorable outcome. The mortality rate with conventional therapy was 86 % compared to 67 % with thrombolysis. The rate of brain hemorrhage with clinical deterioration was 7 % in thrombolysis patients. Schumacher *et al* (17) reported 20 patients with vertebrobasilar occlusion of < 6 h duration treated with upto 1,500, 000 IU local UK plus IV heparin. Recanalization was achieved in 66 %. There was no or minimal deficit in 45 %. The mortality rate was 45 %.

Recanalization rates depend upon the location of the vertebrobasilar occlusion. Distal basilar occlusions have higher recanalization rates than proximal occlusions. The timing of IA vertebrobasilar thrombolysis is often a difficult decision. The presence of coma or tetraparesis for several hours portends a poor prognosis, despite recanalization (16, 18, 19). Such symptoms do not preclude survival, and recovery has been documented after successful recanalization in such patients (18).

The time window for thrombolysis may be longer in the vertebrobasilar circulation. Many series have included upto 24 h (16), 48 h (18) and even 72 h (16) after symptom onset in patients with stuttering courses. Some studies suggested good outcomes in patients receiving delayed treatment (20). A longer time window may be because of a higher ischemic tolerance or improved collateralization in the posterior

circulation. Cross and colleagues (21) found that better collateral blood flow was correlated with improved responses to thrombolysis and with longer tolerance of ischemia. Patients with proximal basilar artery thrombosis did not seem to have the same benefit. Patients with vertebrobasilar ischemia often have chronic atherosclerotic disease which allows collaterals to develop over time.

There may be two distinct populations of patients with vertebro basilar occlusion as hypothesized by Cross *et al.* (21). Patients with a progressive stuttering course may have better collateral circulation and better outcomes despite later treatment than patients with the sudden onset of severe deficits owing to poor collaterals even though they may be brought to treatment earlier.

Table 2

Summary of the major thrombolytic trials
Randomized Trials of Hyperacute Thrombolysis in AIS

Name of study	Onset to treatment(n)	No. of patients	Therapy	Route	Dose
NINDS rtPA Stroke trial	≤ 3	624	rtPA	IV	0.9 m/kg over 1h
ECASS I	≤ 6	620	rtPA	IV	1.1 mg/kg over 1h
ECASS II	≤ 6	800	rtPA	IV	0.9 mg/kg over 1h
ATLANTIS A & B	≤ 5h ≤ 6h	613 142	rtPA	IV	0.9 mg/kg over 1h
PROACT II	≤ 6 h	180	Pro – UK + heparin	IA	9 mg over 2h
ASK	≤ 4 h	340	SK	IV	1.5 Million units over 1h
MAST I	≤ 6 h	622	SK	IV	1.5 Million units over 1h
MAST E	≤ 6 h	310	SK	IV	1.5 Million units over 1h

A major issue regarding access to IA thrombolysis to treat acute ischemic stroke is that it requires the ready availability of a neuro interventionalist and a tertiary stroke team. Such expertise is not currently available in most community hospitals. Another limitation of IA thrombolysis is the additional time required to begin treatment compared to intravenous thrombolysis. There are also concerns regarding the invasiveness of the technique and procedural risks not inherent to IV thrombolysis. However, serious procedural complications were uncommon in PROACT I & II trials.

Meta - Analysis

Two meta-analysis included data of several thrombolytic trials. Hacke *et al* (22) evaluated the data of the NINDS trial and both ECASS trials including 2044 patients (1034 – rtPA, 1010 – placebo). The effects of rtPA treatment on reducing disability and death (mRS score = 2 vs = 3), on the occurrence of symptomatic ICH and on mortality were evaluated. The analyses were stratified for both time windows: 0 to 3 and 0 to 6 hours. For the 3 hour time window, there was a 45% reduction of unfavorable outcome (OR, 0.55; 95% CI, 0.41 to 0.72); risk for ICH was significantly increased among rtPA – treated patients (OR, 2.68; 95% CI, 1.56 to 4.62); mortality associated with ICH was not increased (OR, 0.91; 95% CI, 0.63 to 1.32). For the 6 hour time window, there was a 3% reduction of disability and death (mRS score = 3) (OR, 0.63; 95% CI, 0.53 to 0.76); risk of ICH was significantly more in rtPA treated patients (OR, 3.33; 95% CI, 2.39 to 4.37), but mortality was not different between rtPA treated patients and controls (OR, 1.07; 95% CI, 0.84 to 1.36).

In the Cochrane Library, all randomized, placebo – controlled trials of any thrombolytic agent in patients with ischemic stroke were included (23) (NINDS trial, ECASS I and II, ATLANTIS A and B, PROACT I and II, ASK trial, MAST – E, MAST – I and several smaller trials). There were 5216 patients in 17 trials, 2889 of them from rtPA trials. Thrombolytic therapy significantly increased the odds of death within the first 10 days (OR, 1.85; 95% CI 1.48 to 2.32). The main cause of the increase in deaths was fatal ICH after thrombolysis (OR, 4.15; 95% CI, 2.96 to 5.84). Despite this, thrombolytic therapy, administered up to 6 hours after onset, significantly reduced the proportion of patients who were dead or dependent (mRS score = 3) (OR, 0.83; 95% CI, 0.73 to 0.94). For patients treated within 3 hours of stroke,

thrombolytic therapy appeared to be more effective (OR, 0.58; 95% CI, 0.46 to 0.74). Trials testing intravenous rtPA suggest that it may be associated with a lower mortality when given up to 6 hours after onset (OR, 1.24; 95% CI, 0.85 to 1.81). A meta-analysis with only the data of trials using intravenous rtPA for thrombolytic therapy in the 3 to 6 hour time window has not yet been published. An analysis of the appropriate data for this time window concerning dependence or death (mRS = 3) from ATLANTIS, ECASS and ECASS II, leading to an OR of 0.79 (95% CI, 0.66 to 0.96) in favor of rtPA is given in Table 4 (24).

Table 3

Meta analysis of data concerning a 3 – 6 hour time window from ATLANTIS, and ECASS

Study	rt PA	Placebo	Fisher's Exact *P*	OR	95 % CI
ATLANTIS	120/272	126/275	0.73	0.93	0.67-1.30
ECASS-I	170/226	192/279	0.24	0.80	0.56-1.15
ECASS-II	140/328	163/314	0.02	0.69	0.51-0.94
Sub Total	430/866	481/868	0.02	0.79	0.66-0.96

Since 1995, the number of patients in randomized controlled trials of thrombolysis for acute ischemic stroke has more than doubled, bringing the total of 5210 patients in 17 trials including 2955 in 8 trials of rtPA. Cumulative analysis confirms that there are net benefits despite the definite hazards. For every 1000 patients treated with rtPA upto 6 hours, ~ 55 more patients will be independent at the end of follow-up including the cost of ~ 20 extra deaths. The number – needed – to – treat (NNT) to prevent one death and disability with in 3 hour time window with rtPA is 7 or 8. Similar NNT with in 6 hour time window increases to 17 and for the 3 to 6 hour time window, it is 25. However, the statistical heterogeneity and wide CIs indicate that these estimates of rtPA effects are unreliable. The true effect of rtPA might be considerably better or considerably worse than suggested here. ECASS – III was designed to confirm the superiority of rtPA over placebo for patients with ischemic stroke when administered within a time window from 3 to 4 hours from the onset of symptoms. The study is being

performed in 80 sites in 15 European countries. IST–3 study reassesses the role of rt – PA in patients with symptoms lasting less than 6 hours.

Recommendations (25)

The current recommendations are based on the hierarchy of evidence drawn from meta and pooled analysis of randomized controlled trials, individual clinical trial data, formal phase IV studies, and reports from routine clinical practice, and incorporate the accepted importance of early treatment. Based on currently available data, and the principle of early therapy, it is appropriate to provide recommendations based on the time to treatment (0 to 3 hours, 3 to 6 hours, or 0 to 6 hours), the specific thrombolytic agent (tPA, SK, r- proUK) and the route of administration (IV, IA).

I. For eligible patients, of IV rtPA in a dose of 0.9 mg/Kg (maximum of 9 mg), with 10% of the total dose administered as an initial bolus and the remainder infused over 60 minutes, is recommended, provided that treatment is initiated within 3 hours of clearly defined symptom onset (Grade IA).

II. For unselected patients with AIS > 3 hours but < 6 hours, clinicians are recommended not to use IV rtPA (Grade 2 A).

III. For patients with AIS, clinicians are recommended against the use of SK (Grade IA).

IV. For patients with angiographically demonstrated MCA occlusion and no signs of major early infarction on the baseline CT scan, who can be treated within 6 hours of symptom onset, intra-arterial thrombolytic therapy with rtPA is recommended. (Grade 2 C).

V. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, intra-arterial thrombolysis with rtPA is recommended (Grade 2 C).

Concept of Ischemic Penumbra and Expansion of Therapeutic Time-Window

After vascular occlusions, there is a heterogenous depression of cerebral blood flow (CBF) in the territory of the occluded artery. The penumbra is identified as the brain region receiving regional CBF (rCBF) between two critical values (26, 27). The first, higher, critical value is associated with neuronal paralysis: brain areas receiving rCBF less than 18 – 20 mL/ 100g/ min do not function. The second, lower, critical value is associated with cell death; brain areas receiving less than 8 – 10 in L/ 100g/ min do not

survive, and this area becomes the core of the infarction (26). Neurons in the penumbra are sometimes identified as "idling" to suggest that they are salvageable, although the mechanism of such a phenomenon is unknown. The time course of cell death in the core is rapid where as cells in the penumbra may survive up to several hours (28).

Baron obtained elegant data using positron emission tomography (PET) scanning to explore the penumbra concept. They showed that overtime after stroke an area of excessive oxygen extraction, perhaps reflecting the core, does enlarge (29). However, the temporal evolution of the penumbra can be highly variable. In some patients, a penumbra could be identified upto 48 hours (30) and in others there was no penumbra by 5 hours. Similar sorts of experiments using magnetic resonance imaging (MRI) of water diffusion (DW), a possible marker of the penumbra have also demonstrated the classic DWI – PWI mismatch, representing penumbra. The exact duration of survival is unknown, and likely different under differing circumstances. Cells in zones receiving 10 to 20 cells/ 100g/min are likely to survive for hours, but the number of hours is not known. Many factors may reduce the time such marginally perfused cells can survive. For example, it is known that hyperthermia of 1 or 2^0 C will accelerate cell death (31). Elevations of serum glucose also accelerate cell death (32). Pending recanalization and restoration of blood flow, a number of therapies could be directed at idling neurons in the penumbra. Such neuroprotectants might salvage brain by preserving neurons until blood flow is restored.

The therapeutic window for rescuing ischemic but still viable brain tissue is amenable for many patients. Neuronal death and brain infarction evolves progressively in a time – dependent fashion, but is determined by the duration and severity of the ischemic insult, the underlying cause of ischemia as well as the rate of recanalization. Therapeutic strategies designed to restore cerebral perfusion in a timely fashion, have the potential to limit, the cellular, biochemical and metabolic consequences of cerebral ischemia that ultimately lead to irreversible brain injury. It may be that the survival of the bulk of ischemic tissue is dependent upon early energy failure and ionic imbalances, whereas smaller volumes are dependent upon neurotoxic and inflammatory processes and even less on apoptosis. The concept of 'time is brain" is generally a good one, regardless of what intervention is planned.

Stroke MRI (33 - 36)

A substantial amount of information now is available from PET and MRI studies that potentially salvageable ischemic tissue exists in some patients for many hours after stroke onset. PET availability is limited and the technique is time consuming and hence likely to remain an imaging tool restricted to research centers. Diffusion-perfusion MRI and CT perfusion studies are now widely available at many clinical facilities. The PWI – DWI mismatch on MRI provides a rapidly identifiable imaging marker of potentially salvageable ischemic tissue that can be widely used to identify potentially treatable ischemic stroke patients irrespective of time from onset. Hopefully, using this approach, to identify, patient's therapy will move patient selection to a pathophysiologically based assessment and away from rigid time windows. This should expand the therapeutic time window for both thrombolysis and neuroprotection.

In the future, perfusion and diffusion absolute value maps are likely to be generated, and estimations provided as to what percentage of ischemic tissue is highly likely to be irreversibly injured, what percentage is not at a risk of infarction, and what percentage is at risk for infarction but can be salvaged with appropriate treatment. The availability of such a three–compartment assessment of ischemic tissue will move acute stroke treatment into a new era of "time – independent" decision making.

DWI may delineate infarcted brain tissue within minutes, although there is grouping evidence that in the very early stage of stroke there may be reversible DWI changes in up to 45 % of patients experiencing recanalization after treatment with rtPA (37-40). However, these lesion reversals in most instances are only minor or partial and are quite frequently not permanent. Contradictory data exist about whether a DWI/ apparent diffusion coefficient threshold for irreversible ischemia exists (40 - 42). PWI defines the area of cerebral hypoperfusion. The absolute volume difference or ratio of PWI and DWI reveals the ischemic tissue at risk of irreversible infarction (43, 44). The presence of a vessel occlusion on MRA is associated with a PWI/ DWI mismatch. Therefore, stroke MRI defines the ideal candidate for thrombolysis (45-48). In addition, early recanalization achieved by thrombolysis results in significantly smaller infarcts and a significantly better clinical outcome (49, 80). A

prospective, open–label, non randomized multicenter trial examined the MRI baseline characteristics of patients with acute ischemic stroke and studied the influence of intravenous rtPA on MR parameters and functional outcome in 139 patients (76 rtPA versus 63 controls) within 6 hours after symptom onset and on follow–up(47). Patients treated with rtPA were significantly more severely affected at baseline but still had a non significant trend toward smaller infarctions and a significantly better clinical outcome (mRS ≤ 2) regardless of the time of rtPA treatment (≤ 3 hours or 3 to 6 hours). Therefore, stroke MRI–guided rtPA therapy appears to be safe and effective beyond a 3 hour time window. Furthermore, the rather strictly defined therapeutic window may be qualified and individualized according to the findings in each patient. An interesting observation is the persistence of a PWI/ DWI mismatch even > 24 hours after stroke onset (46, 50). This implies that a late recanalization may be beneficial for a patient with tissue at risk and a persisting vessel occlusion, as shown in individual patients (51). Additionally, a protracted metabolic recovery after thrombolysis may still be associated with a good clinical result (52). Stroke MRI may be useful in identifying patients with extensive infarctions with or without a PWI/ DWI mismatch, which, if present, may be salvaged by more aggressive therapies (53-55).

CT/ CT Angiography [CTA] – source Images [CTA – SI] (56 - 58)

A new instrument for the improvement of CT rating is ASPECTS (Alberta Stroke Program Early CT Score). ASPECTS studies divide the MCA territory into 10 regions of interest as seen on 2 standardized axial CT slices (basal ganglia and lateral ventricles). The whole MCA territory is allotted 10 points (1 for each area), and a single point is subtracted for each of the defined regions if ischemic lesions are seen. The baseline ASPECTs value correlated inversely with the severity of stroke on the NIHSS Cr = 0.056, P < 0.001) and predicted functional outcome and symptomatic ICH (P < 0.001; P = 0.012). A sharp increase in dependence and death occurs with an ASPECTs value ≤ 7. A comparison of CT/CTA/CTA–SI findings with MRI (DWI) and MRA reveals equal accuracy of CTA and MRA close to equal accuracy of infarct volumes according to CTA- SI compared with DWI, and a predictive value of poor collaterals for infarct growth. Therefore, CT/ CTA/ CTA–S1 may render information similar to that of PWI/ DWI mismatch concept.

Combined IV & IA thrombolysis (59, 60)

Combined IV and IA delivery of thrombolytic drug has several potential advantages. First, a combined approach looks to start IV thrombolytic therapy as quickly as possible in order to minimize the time from stroke onset to recanalization. The addition of IA therapy following IV rt PA has the advantage of demonstrating whether or not a clot is still present and whether more thrombolytic drug or other methods to recanalized the occluded artery are needed.

The Emergency Management of Stroke (EMS) or the bridging Study, was designed to test the feasibility and provide preliminary data regarding the relative benefits and risks of combined in rtPA (0.6 mg/kg over 30 min) and IA rtPA therapy (administered only if a clot was demonstrated by angiography at a dose of up to 20 mg at the site of the clot over 2 hours), as compared to IV placebo and IA rtPA therapy. Intravenous treatment in the EMS study had to be started within 3 hours of onset. The inclusion/exclusion criteria for the EMS pilot trial were identical to that of the NINDS rtPA randomized trial except that patients had to have an NIHSS of 5 or more. The total number of patients in the EMS study was small (total n = 35, combined IV/IA rtPA group = 17 and IV placebo and IA rtPA =18). The pilot study was not powered to examine differences in efficacy between the two treatment groups. Despite the imbalances in the baseline NIHSS scores between the two treatment groups, recanalization in combined IV/ IA rtPA treatment groups was more complete than recanalization in the IA alone group, although the difference was not significant. For these patients who had a clot at angiogram, recanalization was significantly greater in the combined IV/ IA group than in the IA alone group. The proportion of improved outcomes (prospectively defined as a seven point improvement of the NIHSS at 7 – 10 d) was not significantly greater in combined IV/ IA treatment group as compared to IA alone group (both groups = 24 %). There were no symptomatic or asymptomatic intracerebral hematomas in the 35 EMS patients. The data illustrated that a combined approach can help to minimise the time to treatment and recanalization, can be used to help titrate the amount of thrombolytic drug and is feasible in clinical practice. Interventional Management of Stroke (IMS) Study was similar in design to EMS Bridging Trial. IMS – II is currently underway and is investigating the risks and benefits of

combined IV/ IA rtPA plus low – energy ultrasound in ischemic stroke patients with an NIHSS ≥ 10, in whom treatment is started with in 3 hours of onset.

Combination of Thrombolytic Therapy with Neuroprotection (61-73)

Till date only two studies designed to evaluate the effect of combining thrombolysis and neuroprotection have been carried out, and one was terminated prematurely. In patients given intravenous rtPA within 3 hours of stroke onset according to NINDS protocol, lubeluzole had to be started 1 hour of starting rtPA. Although the number treated (80 – 90) was too small (due to premature termination) to draw definite conclusions, there was no evidence of benefit. However, the study demonstrated that such a trial design is feasible. A small study was designed to test the combination of rtPA given within 3 hours and clomethiazole given within 8 hours. The study included 97 patients given clomethiazole and 93 patients given placebo, all patients received rt – PA first according to NINDS protocol. Overall, there was no benefit seen. In the patients with the worst strokes however, there was a possible effect. These results suggest that clomethiazole may augment the beneficial effect of rtPA in patient with large strokes. Although still unproven as a means to improve on results obtained with thrombolytic therapy alone, combination therapy of thrombolysis with neuroprotective drugs has a sound theoretical and experimental basis. Although one possible benefit of such an approach may be to extend the therapeutic time window, any such combination should be started as early as possible after the onset of stroke symptoms, and it is likely that the neuroprotective agent will be most effective if it is administered before or along with lytic therapy.

Newer Thrombolytic Agents

One of the two major problems in crossing 3 – hour window is the propensity to intracerebral hemorrhage. Several second and third generation thrombolytic agents (tenecteplase, reteplase, desmoteplase, plasmin, microplasmin) are being tested. The goal is to create new thrombolytic agents with longer half–lives that permit bolus administration, with improved rates of restoration of flow and with reduced rates of ICH.

Desmoteplase: The recently completed phase–II-B (DIAS) Desmoteplase in Acute Stroke) study of a rtPA molecule derived from bat saliva

used diffusion/ perfusion MRI to enroll patients and to assess the biological activity of different doses. Patients were included in the study between 3 to 9 hours after stroke onset, if they demonstrated a perfusion lesion volume ≥ 20 % above the baseline diffusion lesion volume. MRA was also performed and all 3 MRI modalities were repeated several hours after completion of the thrombolytic therapy to evaluate reperfusion efficacy. Lower, weight–adjusted dosing demonstrated a very reasonable safety profile and quite dramatic reperfusion efficacy. Clinical outcome tended to be more favorable in treated patients as well. This pilot study is important because it confirms the safety of weight – adjusted desmoteplase in ischemic stroke patients when given upto 9 hours after, stroke onset as well as the intended biological effect of inducing reperfusion.

Tenectplase: TNK – tPA is a more fibrin specific variant of tPA. It also has a longer half – life and increased resistance to plasminogen activator inhibitor type I that allows for dosing as a single bolus. Pilot studies are underway.

Combination of Glycoprotein (GP) IIb/ IIIa Inhibitors with Thrombolysis: GP II b/ III a inhibitors block the final common pathway of platelet aggregation, and have demonstrated efficacy in preventing thrombus formation in acute coronary syndromes and percutaneous coronary interventions. In acute ischemic stroke, a dose – escalation study demonstrated that the GP II b/ III a inhibitor aboiximab is safe when given as a 0.25 mg/kg bolus and 0.125 mg/kg/ minute infusion. Abciximab in Emergent Stroke Treatment Trial (ABESTT) study suggests possible efficacy of abciximab in acute, stroke, with a longer therapeutic window and a better safety profile than rtPA within 3 hours. A phase 2 trial is underway in acute ischemic stroke of less than 6 hours duration. Some centers are using Gp IIb/ IIIa inhibitors as adjunctive therapy with intra – arterial thrombolysis in AIS.

Mechanical Clot Lysis: Mechanical approaches to ischemic stroke are attractive because they may obviate the need for thrombolytic drugs that increase the risk of reperfusion hemorrhage. The angiojet catheter has been used to fragment and suck in the clot. It uses a high-velocity stream of saline directed back into the catheter to create a localized, low-pressure zone at the distal tip. Via the Bernoulli effect, thrombus is trapped, broken up into small particles, and evacuated, literally within minutes. The system is currently

approved for use in saphenous vein graft thrombectomy but has been modified for neurovascular use. A problem has been distal embolism of particles. Other means of delivering energy to fragment the clot are being developed, including the use of ultrasound and laser devices. The current limitation of these mechanical devices is their relatively larger catheter size & less flexibility, which limit access to the tortuous vessels of the intracranial circulation. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial is underway to evaluate the safety of the MERCI Retriever System. There are a few other smaller studies such as EKOS, TRUMBI and CLOT BUST that evaluate if there are additional benefits when thrombolytics are used in combination with ultrasounds exposure. Theoretically, this approach would increase the accessibility of the drug to the clot.

The search for Neuroprotective strategies in stroke (61-85)

Neuroprotective strategies can be divided into those that limit ischemic cascade or those that reduce reperfusion injury. Neurons die under ischemic conditions when delivery of oxygen and an energy source are not sufficient to meet their metabolic demands. Therefore, ischemic neurons must either receive increased blood flow or their metabolic demands need to decrease. The most important step in limiting ischemia is the quick restoration of blood flow that occurs either naturally or with the aid of thrombolytics such as rt-PA. Before complete restoration of blood flow, therapies such as hypothermia may decrease metabolic demand and extend neuron survival. Once depleted of energy, membrane-bound ion pumps fail, leading to membrane depolarization, sodium and calcium entry, and neurotransmitter release. Dendritic glutamate release activates down stream neurons, leading to calcium entry, cellular damage, apoptosis, and further release of toxic molecules. Agents that modulate ion channels and glutamate receptors target this pathway. Reperfusion injury was observed by comparing infarct volumes in animal models of transient and permanent ischemia. Reperfusion, while critical to limit ischemia, contributes to cell death by enhancing production of free radicals, inflammation and blood-brain barrier breakdown; each has been targeted by therapies. However, all the human trials on neuroprotection have been negative thus far.

On the basis of complexity of events in cerebral ischemia and the disappointing results from single-agent trials, it may not be realistic to expect that a single neuroprotective drug will have lasting benefit. Rather, effective neuroprotection may require "rational" polytherapy that combines drugs with different mechanisms of action, perhaps administerd at different poststroke intervals, to maximize efficacy and/or extend the window for reperfusion, minimize reperfusion injury or hemorrhage, or inhibit delayed cell death. Furthermore, because the failure if several neuroprotective trials has been attributed to dose-limiting toxicity, combination therapy may permit lower doses of each agent and minimize adverse effects. Combinations with nonpharmacological neuroprotective strategies such as hypothermia, insulin, and blood pressure control should also be subjected to clinical trials.

Combined thrombolysis-neuroprotective approaches have shown promise in animal studies and are beginning to be investigated in clinical trials. For example, synergistic effects have been demonstrated in animals when thrombolysis is combined with citicholine, an AMPA antagonist, an NMDA antagonist, or other agents. Administration of antileukocytic adhesion antibodies has been shown to extend the therapeutic window for thrombolysis. Recently, 2 trials have demonstrated the feasibility and safety of intra-venous t-PA treatment followed by neruoprotectant administration: the CLASS-T trial of clomethiazole and a study of lubeluzole.

In animals, synergy has been demonstrated by the combination of 2 neuroprotective agents with different actions; some examples include the NMDA antagonist MK-801 in combination with a GABA agonist, a free radical scavenger, a calcium antagonist, citicholine or basic fibroblast growth factor (bFGF). Similarly, synergy has been observed with the combination of the antioxidant tirilazad and magnesium, the combination of 2 different antioxidants and citicholine combined with bFGF.

Synergistic effects on infarct size and therapeutic window have also been found in animals through the use of antiexcitotoxic agents in combination with antiapoptotic agents, eg., the NMDA antagonist dextrorphan plus the protein synthesis inhibitor cyclohexamide, or MK-801 with the caspase inhibitor ZVAD –fmk. Caspase inhibitors given with bFGF extended the therapeutic window and lowered the required doses for neuroprotection.

Hypothermia (86-89)

It has been well documented that mild (34°C) to moderate (32°C) systemic hypothermia protects brain from some ischemic damage in various animal models. Although the exact mechanisms are unknown, a reduction of body temperature, especially brain temperature, may lead to reduced cerebral oxygen consumption, decreased intracellular lysosomal enzyme activity, suppressed free radical formation, protection of the fluidity of the cell membranes, reduced intracellular acidosis, and inhibition of cell damage mediated by excitatory neurotransmitters.

Several clinical studies suggested that mild hypothermia improved neurologic outcome in patients after cardiac arrest. A case-control multi-center trial demonstrated that cardiac arrest patients who were treated with mild externally applied hypothermia (33°C) had significantly better neurological outcome and less mortality than those who were maintained normothermic. Acute hyperthermia, on the other hand, has been associated with a higher mortality rate 1 year post-cardiac-arrest, as compared to normothermic patients.

Recently, Krieger *et al*(88) published a pilot study, investigating moderate hypothermia therapy in ischemic stroke. Nineteen patients with major acute ischemic stroke (NIHSS>15) were randomly assigned to either hypothermic (32°C) or control (maintained normothermic) groups. Patients in the hypothermic group were subjected to surface cooling with a cold blanket. The therapeutic window for hypothermic treatment was 6 h after stroke onset, and thrombolytic therapy was given whenever patients were eligible. Although complications such as bradycardia, ventricular ectopy, hypotension, melena, infections, and rebound hyperthermia were observed, the treatment was considered safe.

There are two main obstacles to surface cooling hypothermia: slow induction and intense patient shivering. To overcome these problems, endovascular cooling was introduced. In general, a catheter with a closed-loop circulation system embedded was attached to a temperature controlling system. The catheter was then inserted in the inferior vena cava to cool circulating blood and regulate body temperature. Georgiadis *et al*(89) reported 6 patients who suffered severe acute ischemic stroke and were treated with endovascular hypothermia. During the hypothermia, the minimal temperature achieved was 32.2°C. According to their study, the procedures

were safe, and the adverse effects were similar to those encountered in surface cooling. To further evaluate its safety and efficacy, several clinical trials are currently being conducted.

Combination of Hypothermia with thrombolysis:

COOL AID trial (cooling for Acute Ischemic Brain Damage) is a phase 2 trial in patients with acute ischemic stroke of less than 12 hours duration. After thrombolysis, a heat exchange catheter is introduced into the inferior vena cava, without need for paralysis or sedation that may account for much of the medical comorbidities seen with other methods of hypothermia. The body is cooled to 32^0 C.

Besides the advances in understanding stroke pathophysiology and development of newer means to reperfuse and apply a comprehensive multipronged approach in salvaging the jeopardized and critically perfused brain tissue, it is increasingly being recognized that provision of specialist stroke services and stroke units is associated with reduction in mortality, dependency and subsequent need for institutional care. Although it is not clear precisely which aspects of care are associated with these improvements, there is accumulating evidence that the process of care delivered by specialist stroke teams is significantly different from that of conventional care. The importance of physiological monitoring following stroke may be reflected in the fact that up to 40% of acute stroke patients suffer neurological deterioration shortly after admission to hospital. This neurological deterioration may be consequent upon natural progression of the initial stroke, but in part may also be due to changes in physiological variables such as glucose, oxygen saturation, temperature and blood pressure. Specialist stroke care, while based upon very simple principles, appears to be highly effective; comprehensive multidisciplinary assessment including the early assessment and management of swallowing disorders, early maintenance of hydration and nutrition and early mobilization underpin the principles of acute care.

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