Thrombolytic Therapy Should be The First Line Treatment in The Management of Acute Ischemic Stroke

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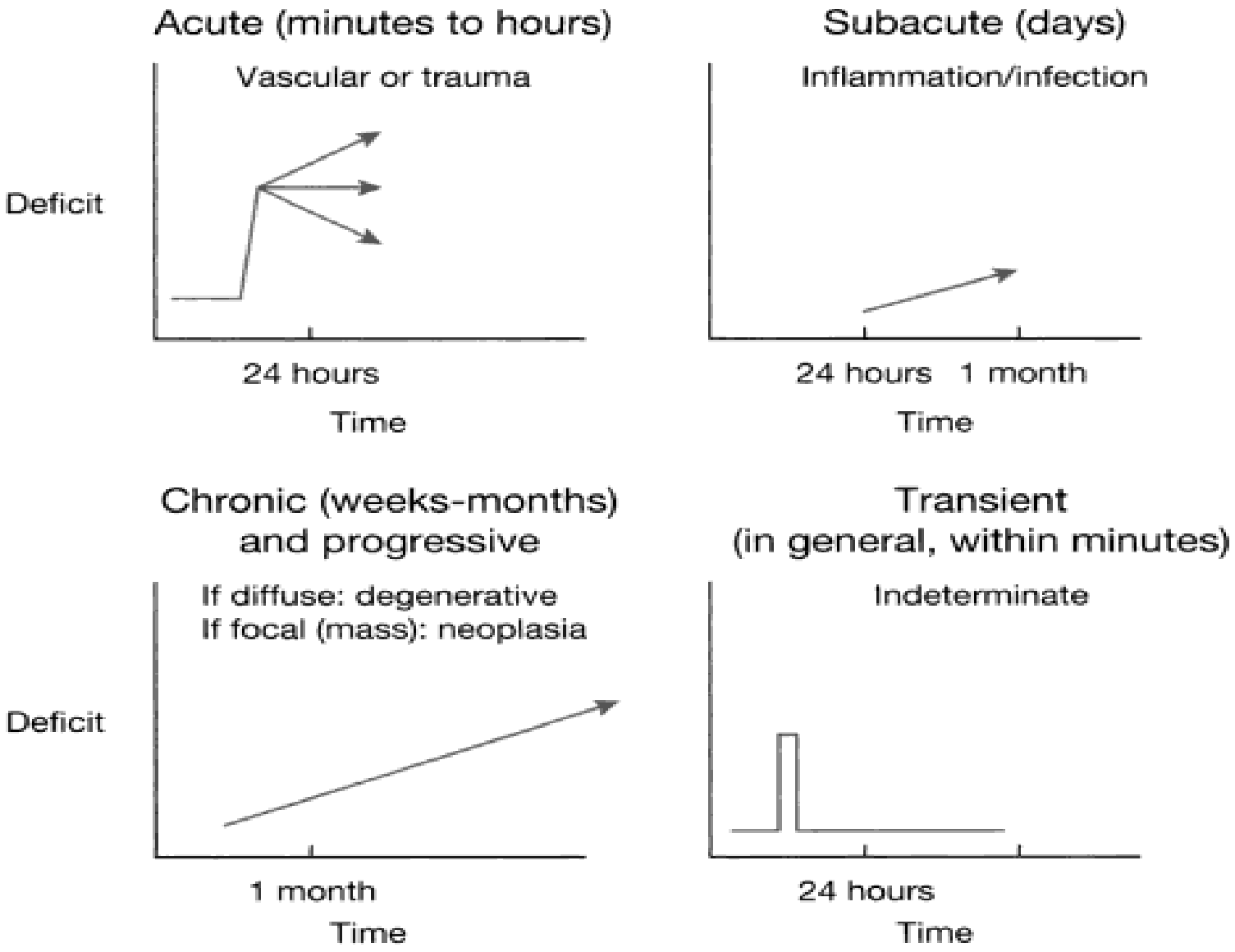

Temporal profiles of neurologic deficits that point to the underlying pathologic cause.

-Mayo Clinic

Ischemic Stroke

- **Sudden onset of a non-convulsive, FND due to CVD**

- *Embolic strokes*
  - Deficit reaches its peak almost at once
  - Reverses itself within a **few hours or days**

- *Thrombotic strokes*
  - Evolve more slowly over a period of several min/hrs and occasionally days
  - Improve gradually over **weeks or months**

- *Cerebral Hemorrhage*
  - There is severe deficit of rapid but not necessarily instantaneous onset

Thrombotic

- 1/3 of ischemic strokes, occlude large cerebral arteries (ICA, MCA, basilar), small penetrating arteries (lacunar strokes), cerebral veins, and venous sinuses.
- Symptoms evolve over minutes to hrs.
- Often preceded by TIA in same territory causing similar deficits.

Ischemic Stroke: Embolic

- Proximal origin of clot
- Occurs at any time
- Frequently during periods of vigorous activity
- History of AF, valvular vegetations, thromboembolism from MI, ulcerated plaques in carotid system
- Seizures in 20% of cases

Embolic

- 2/3 of ischemic strokes, from thrombus in heart, aortic arch, large cerebral artery or medium sized branches of brain a.
- In anterior circulation usually effect MCA , in posterior circulation usually effect branch point of basilar or PCA.
- Produce maximal neurological deficit at onset.
- When TIAs precede, symptoms vary because emboli lodges in different places.

Table 361-1. Pathophysiologic Classification of Cerebrovascular Diseases

Stroke Subtype	Frequency, %	CT Findings	Causes
Ischemic	85		
Thrombotic	25		
Lacunar stroke	20-25	Hypodensity usually <1 cm^3	Lipohyalinosis of small vessels
Large vessel	1-5	Varies	Atherosclerosis of intracranial arteries
Embolic	75		
Cardioembolic	20	Wedge-shaped cortical/subcortical hypodensity	See Table 361-2
Artery-artery	15	Wedge-shaped cortical/subcortical hypodensity	Aortic, carotid or intracranial atherosclerosis
Cryptogenic	30	Wedge-shaped cortical/subcortical hypodensity	Extensive workup reveals no cause
Other	10	Varies	
Hemorrhagic	15		
Intraparenchymal	10	Hyperdensity within brain substance	Hypertension, AVM, amyloid angiopathy
Subdural	<1	Hyperdensity within subdural space	Trauma
Epidural	<1	Hyperdensity within	Trauma
Subarachnoid	1-2	Hyperdensity within subarachnoid space	Ruptured aneurysm, trauma

NOTE: AVM, arteriovenous malformation; CT, computed tomography.

Acute Ischemic Strokes
Objectives

- Acute Management
  - Thrombolytic Therapy (resolution)
  - Antithrombotic Therapy (reduce progression and recurrence, and prevent VTE)
- Secondary Prevention
  - Antiplatelet therapy

PROACT II Trial

- First phase III trial of I.A.T.
- Pro-UK + heparin vs IV heparin within 6h.
- 180 patients, M1 or M2 MCA occlusion.
- Average NIHSS 17.
- Median time to I.A.T 5.7 hours.

PROACT II Trial

- mRS < 2 : 40% VS 25% (+- SIG)
- Recanalisation at 2h: 66% vs 18%
- Hemorrhage at 36h:
  - all: 46% vs 16%
  - symptomatic: 10% vs 2%
- No difference in mortality

I.A.T. Rate of Recanalisation

- PROACT II :66% overall
- Urbach et al 2002:

  Thrombus 53%: 23% carotid T,

  74% distal M1

  60% M2

NINDS results

- No significant differences in Mortality at 3 mos or 1 year (24% vs 28%)
- Complete or near complete recovery at 3 months was 38% with tPA and 21% with placebo (ARR-17%, NNT~6)

Outcomes at 90 days	Alteplase	Placebo	Relative change	NNT/H
Modified Rankin 0 to1	52%	45%	19%	12
Barthel Index >95%	63%	59%	8.4%	NS
NIHSS 0 to 1	50%	43%	16%	15
Glascow Outcome Scale of 1	51%	45%	12%	NS
ICH	27%	18%	53%	11
Symptomatic ICH	2.4%	0.2%	864%	47

Do we thrombolyse or is this just a TIA?

- 312 pts randomized to placebo group in the NINDS trial
- Medial time to treatment was 90 minutes
- Only 2% were symptom free at 24 hours
- “unlikely that patients with a persistent neurologic deficit of longer than 90 minutes will resolve spontaneously”
  - Borg KT et al TIA: an emergency medicine approach. Emergency Medicine Clinics of North America. Vol 20, 3, Aug 2002

Hx and Physical

"in general, the diagnosis of stroke is straightforward"

- Emergency physicians correctly identified 152 or 176 consecutive stroke patients (sens 86.4%) and 1818 of 1835 patients without stroke (spec 99.1%)
  - Von Arbin M et al. Accuracy of bedside diagnosis in stroke. Stroke. 1981: 12:288-293

Anticoagulants?

- Several studies with heparin, LMW heparins, heparinoid
- Conclusion:
  - parenterally administered anticoagulants are associated with an increased risk of serious bleeding complications (level I)
  - early administration of the rapidly acting anticoagulants does not lower the risk of early recurrent stroke, including among patients with cardioembolic stroke (level I)

Anticoagulants

- Recommendations:
- Urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended for the treatment of patients with acute ischemic stroke (grade A)
  - Guidelines for the Early Management of Patients With Ischemic Stroke. A Scientific Statement From the Stroke Council of the American Stroke Association. Adams HP et al *Stroke.* 2003;34: 1056-1083

Antiplatelets

- 2 large trials with aspirin:
  - Chinese Acute Stroke Trial
  - International Stroke Trial

Chinese Acute Stroke Trial (CAST)

- Prospective, randomized, placebo controlled trial of >21000 pts, where ASA 160mg/day or placebo was given within 48h of stroke onset
- Aspirin reduced early mortality
  - 3.3 vs 3.9%;
- No effect on the proportion of patients who were dead or dependent at hospital discharge
  - 30.5 vs 31.6%; *p*=0.08
  - (CAST: randomized placebo-controlled trial of early aspirin use in 20000 patients with acute ischemic stroke. Lancet 1997; 349: 1641-1649

International Stroke Trial (IST)

- Prospective, randomized, open-label trial of ASA and unfractionated heparin in >19000 pts
- half received ASA and half were instructed to avoid ASA, then half of pts in each group received unfractionated heparin
- Significant reduction in recurrent events but acute mortality was not reduced (level I)
- Small significant (0.1% absolute) significant increase in the incidence of intracranial hemorrhage (level I)
  - IST: a randomized trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. Lancet 1997;349:1569-1581

NINDS

- multicentre, randomized, placebo-controlled trial
- 624 patients with ischemic stroke were treated with intravenous t-PA (0.9 mg/kg) within 3 hours of the onset of stroke symptoms.
- Part 1: primary endpoint was neurological improvement at 24h (complete neuro recovery or improvement of 4 points or more on NIHSS)
- Part 2: primary end point was global odds ratio for favorable outcome (defined as complete or nearly complete neurological recovery at 3 months after stroke)

NINDS

- Part 1: t-PA recipients did not suddenly improve, and there were no significant outcome differences at 24 hours
- Part 2: patients treated with t-PA were more likely to have a favorable neurological outcome at 90 days (odds ratio 1.7; 95% CI, 1.2-2.6; p=0.008)
- Compared to controls, t-PA recipients had a 12% absolute (32% relative) increase in the proportion with minimal or no disability

ECASS

- compared rtPA (1.1 mg/kg) to placebo in patients with <6 hours of symptoms
- early intracranial hemorrhage, fatal cerebral edema and early mortality were more common in treated patients than in controls
- surviving t-PA recipients were more likely to have minimal or no disability at 3 months
- authors concluded: while some patients benefit, the rate of negative outcomes was prohibitively high
- Intravenous rtPA was not more effective than placebo in improving neurological outcomes at 3 months after stroke (level I)
  - Hacke W, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke, the European cooperative acute stroke study (ECASS). JAMA 1995;274:1017-25

ECASS vs NINDS

- ECASS: higher dose, longer window of treatment
- Post hoc analysis concluded that pts treated within 3 hours appeared to benefit from rtPA

ECASS-II

- applied the same eligibility criteria and used the same 0.9 mg/kg rtPA dose, but enrolled patients within 6 hours of symptom onset
- More than 1/3 of pts in each group made and excellent recovery and no significant benefit was noted from treatment
- rtPA did **not** significantly increase the rate of favorable 90-day outcomes (40.3% vs. 36.6%, p=0.277), and was associated with a higher incidence of parenchymal hemorrhage (11.8% vs. 3.1%), symptomatic intracranial hemorrhage (8.8% vs. 3.4%), and early death due to intracranial hemorrhage (11 vs. 2 cases)

ECASS-II

- no significant differences in 30- or 90-day mortality
- subgroup analysis showed a trend towards improved neurological outcomes in patients with <3 hours of symptoms, but the numbers were small and statistically insignificant
- ECASS-II therefore failed to reproduce the positive results of NINDS
  - Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D et al. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Lancet 1998;352:1245-51

ECASS-II

- Recruitment bias?
- Avoided recruitment of pts with Multilobar infarctions
- Thus severity of strokes was less than in other trials
- Generally more favorable prognosis may have reduced the likelihood of detecting a therapeutic effect

Cochrane Stroke Group Trials Register

- Up to January 2003
- Objective: assess safety and efficacy of thrombolytic agents in patients with acute ischemic stroke
- Selection criteria: randomized trials of any thrombolytic agent compared with control in patients with definite ischemic stroke

- 18 trials, 5727 patients
- Urokinase, streptokinase, recombinant tissue plasminogen activator, recombinant pro-urokinase
- 2 trials: intra arterial administration
- 16 trials: intra venous administration
- 50% of data from tPA
- Little data over age 80

Thrombolytic therapy:

- For patients treated within three hours of stroke, thrombolytic therapy appeared more effective in reducing death or dependency (OR 0.66, 95% CI 0.53 to 0.83) with no statistically significant adverse effect on death (OR 1.13, 95% CI 0.86 to 1.48)

Cochrane conclusions:

- Overall, thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living.
- The data from trials using rtPA suggest that it may be associated with less hazard and more benefit

The JAMA Network

From: **Thrombolytic Therapy in Patients With Acute Ischemic Stroke**

Arch Neurol. 2000;57(10):1430-1436. doi:10.1001/archneur.57.10.1430

Table 1. Trials of Intravenous Thrombolytic Therapy After Visualization of the Clot by a Cerebral Angiogram

Source, y	No. of Patients	Partial or Total Recanalization, %	Recanalization of MCA Only, %*	Hemorrhagic Infarctions, %	Mortality, %
Mori et al,[3] 1992					
Recombinant tissue plasminogen activator, mg/kg					
1.17	10	50	71	30	0
0.73	9	44	67	56	22
Placebo	12	17	13	33	17
Yamaguchi et al,[4] 1993					
Recombinant tissue plasminogen activator, 0.73 mg/kg	47	57	NA	47	9
Placebo	46	24	NA	47	13

*The time to treatment was 6 hours for all trials. MCA indicates middle cerebral artery; NA, data not available.

Figure Legend:

Trials of Intravenous Thrombolytic Therapy After Visualization of the Clot by a Cerebral Angiogram

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