



THE INTERNET STROKE CENTER

PRESENTATIONS AND DISCUSSIONS ON STROKE MANAGEMENT

Emerging Therapies:

Intra-arterial Thrombolysis, Angioplasty, and Stenting



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Introduction

Summary

- Many endovascular procedures for stroke treatment or prevention are now feasible: *Two are close to prime time*
- *Intra-arterial thrombolysis* for embolic stroke has been proven effective (although no agent yet approved)
- *Carotid angioplasty*: long term benefit not yet established
- On the horizon: mechanical devices, trials of IA lytic agents, trials of angioplasty

The Team

The Team

- Interventional Neuroradiology
- Stroke Neurology
- Vascular Neurosurgery
- Neurological/Neurosurgical Intensive Care Unit

Feasibility: Case Illustrations

Feasibility: Case Illustrations

- Middle cerebral artery thrombolysis
- Vertebral artery origin angioplasty
- Carotid bifurcation angioplasty and stenting
- Intra-cranial angioplasty and stenting after thrombolysis
- Intracranial angioplasty

Thrombolysis: Rationale

Thrombolysis: Rationale

- Thromboembolic mechanism in 80% of acute stroke (most embolic)
- Threshold of ischemia related to level of blood flow and length of time
- Conversely, amount of viable tissue depends on quality of collaterals and duration of ischemia
- These facts are the basis of the rationale for thrombolysis for acute stroke

IV Thrombolysis Trials

IV Thrombolysis Trials

- NINDS t-PA: benefit 0-3 hours
- ECASS: failed 0-6 hours
- ECASS II: failed 0-6 hours
- ATLANTIS: failed 4 -5 hours
- STAT: benefit 0-3 hours

Potential Advantages to IA

Potential Advantages to IA

- Lower total dose/higher local dose of lytic agent
- May achieve greater recanalization rates
- Lower hemorrhage rates
- May have wider therapeutic window

 Washington University in St. Louis
SCHOOL OF MEDICINE

Reference:

Furlan, et al. JAMA 1999; 282:2003-2011

PRO-ACT II

PRO-ACT II

- Randomized controlled trial of local intra-arterial rpro-UK (9 mg over 2 hours) plus low dose iv heparin vs low dose iv heparin (2:1)
- Inclusion: M1/M2 occlusion by angio
- Exclusions: same as NINDS t-PA trial
- Total drug given regardless of benefit at 1 hour
- Endpoints: Modified Rankin score at 90 days

NINDS t-PA Exclusions

NINDS t-PA Exclusions

- Minor stroke (NIH Stroke Scale 0-4)
- Rapidly improving major stroke
- Seizure; concurrent “serious medical illness”
- Acute MI; post-MI pericarditis
- CT with hemorrhage or related low attenuation change
- History c/w acute SAH, even if CT negative
- Pregnant or lactating female
- Platelet count <100,000; PT >15; Coumadin therapy
- BP > 185/110
- Heparin within 48 hours & elevated PTT
- Any prior intracranial bleed
- Head trauma or prior stroke within 90 days
- GI or GU hemorrhage within 21 days
- Major surgery within 14 days
- LP or noncompressible arterial puncture within 7 days

Reference:

Furlan, et al. JAMA 1999; 282:2003-2011

Wolpert S, et al AJNR 1993; 14: 3-13

PRO-ACT II: Results

PRO-ACT II: Results

- 12,323 patients screened
- 476 went to angiography
 - 180 had M1/2 clot and were randomized 2:1
 - 130 had ICA thrombus
 - 100 had no visible thrombus (spontaneous recanalization)
- Mean time to treatment 5.3 hours
- Modified Rankin 0-2 at 90 days: 40% treatment
25% control (p=0.043)

IA Fibrinolytic Agents

IA Fibrinolytic Agents

- All are plasminogen activators
- Urokinase: off the market
- tPA (alteplase): not proven in intra-arterial use and safety profile (hemorrhage) unknown
- pro-UK: not FDA approved or available
- Retevase (reteplase): same as tPA

Posterior Circulation Thrombolysis

Posterior Circulation Thrombolysis

- Natural history poorly defined
- Diagnosis difficult and often delayed; condition relatively rare
- 3 case series for IA thrombolysis, 2 from our institution
 - 24 patients, outcome related to location of thrombus, degree of recanalization

Summary: IA Thrombolysis

Summary: IA Thrombolysis

- Proven efficacy within 6 hours of ictus (but no proven agent available)
- Recanalization rates may be higher than iv
- Case series for posterior circulation thrombolysis: no trial data
- On the horizon: triage based on imaging, mechanical thrombolysis, trials of other lytic agents, combined intravenous/intra-arterial regimens

Reference:
Brown MM, Presented at AHA Stroke Meeting, Nashville, TN, 1999

Carotid Angioplasty and Stenting

Carotid Angioplasty and Stenting

- Technique evolving: improvements in stent design, protection devices
- Case series report similar procedural complication rates as conventional endarterectomy (mixed populations, though)
- Long term benefit, re-stenosis rates remain undefined
- Three trials versus surgery to date, one completed with preliminary results

 Washington University in St. Louis
SCHOOL OF MEDICINE

Reference:
NASCET N Engl J Med 1991;325:445-453

CAVATAS

CAVATAS

- Prospective, randomized, multicenter trial (1992 - 1997)
- Symptomatic patients with >30% stenosis
- 251 PTA, 253 CEA
- 30 day stroke rate equal (10%)
- Long term survival (at 1 year) equal
- Higher rates of peri-procedural complications with surgery
- Higher rates of re-stenosis at 1 year with PTA

Brown MM, Presented at AHA Stroke Meeting, Nashville, TN, 1999

NASCET Results: 70-99% Stenosis

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Two year cumulative risk of ipsilateral stroke

- Medical group (331 patients) 26%
- Surgical group (328 patients) 9%*

* Includes perioperative morbidity/mortality of 5.8%

Two year cumulative risk of major or fatal stroke

- Medical group (331 patients) 13.1%
- Surgical group (328 patients) 2.5%***

** Includes perioperative morbidity/mortality of 2.1%

ACAS Results

ACAS Results

Five year projected cumulative risk of ipsilateral stroke

- Medical group (834 patients) 11.1%
- Surgical group (825 patients) 5.1%*

Five year projected cumulative risk of major stroke or death

- Medical group (331 patients) 25.5%
- Surgical group (328 patients) 20.7%*

* Includes perioperative morbidity/mortality of 2.3%

Angioplasty and Stenting: Summary

Angioplasty and Stenting: Summary

- Single small trial showing equivalence with surgical endarterectomy at one year (CAVATAS)
- Long term benefit in terms of stroke risk reduction, stent patency unknown
- Can be considered for patients with high surgical risk and symptomatic disease
- Randomized trial currently funded (CREST)
- Future: protection devices, trials for intracranial angioplasty

References

Thrombolysis: Frequency of embolic occlusion in acute ischemic stroke

Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. "Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours."

J Neuro Sci 1989;91:311-322

del Zoppo GJ, Poeck K, Pessin MS, et al. "Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke."

Ann Neurol 1992;32:78-86.

Evidence of an ischemic penumbra out to 24 hours

Marchal G, Serrati C, Rioux P, et al. "PET imaging of cerebral perfusion and oxygen consumption in acute ischemic stroke: relation to outcome."

Lancet 1993;341:925-927.

Thrombolysis: Clinical trials

Furlan A, et al., "Intra-arterial prourokinase for acute ischemic stroke - The PROACT II study: A randomized controlled trial."

JAMA 1999;282(21):2003-2011

NINDS rt-PA Study. "Tissue plasminogen activator for acute ischemic stroke."

N Engl J Med; 1995;333:1581-1587.

Haacke W, Kaste M, Fieschi C, et al. "Intra-venous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS)."

JAMA 1995;274:1017-1025.

Sherman DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, Hsu CY, Levy DE. "Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial. Stroke Treatment with Ancrod Trial."

JAMA 2000; 283(18):2395-403

Haacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. "Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators"

Lancet 1998 352(9136):1245-5.

Possible lower rate of recanalization with iv t-PA

Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. "Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group."

AJNR Am J Neuroradiol 1993; 14(1):3-13.

Basilar artery thrombolysis: Case series

Zeumer, Freitag HJ, Zanella F, Thie A, Arning C. "Local intra-arterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (r-TPA)."

Neuroradiology. 1993;35(2):159-62.

Cross DT III, Moran CJ, Akins P, Angtuaco EE, Derdeyn CP, Diringner MN. "Collateral circulation and outcome after basilar artery thrombolysis."

AJNR Am J Neuroradiol 1998; 19(8):1557-63.

Natural history of vertebrobasilar disease

Caplan LR. "Vertebrobasilar disease and thrombolytic treatment."

Arch Neurol 1998; 55:450-1.

Mechanical thrombolysis

Mathie AG, Bell SD, Saibil EA. "Mechanical thromboembolectomy in acute embolic peripheral arterial occlusions with use of the AngioJet Rapid Thrombectomy System."

JVIR 1999;10:583-90.

Nakano S, Yokogami K, Ohta H, Yano T, Ohnishi T. "Direct percutaneous transluminal angioplasty for acute middle cerebral artery occlusion."

AJNR Am J Neuroradiol 1998;19:767-72.

Carotid endarterectomy trials

North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators. "Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis."

N Engl J Med 1991;325:445-453.

Executive Committee of the Asymptomatic Carotid Atherosclerosis Study. "Endarterectomy for asymptomatic carotid artery stenosis."
JAMA 1995;273:1421-1428

Carotid angioplasty: Case series

Yadav JS, Roubin GS, Iyer S, et al. "Elective stenting of the extracranial carotid arteries."
Circulation 1997;95:376-381

Henry M, Amor M, Masson I, et al. "Angioplasty and stenting of the extracranial carotid arteries."
> J Endovasc Surg 1998;5:293-304.

Intracranial angioplasty: Case series

Connors JJ III, Wojak JC. "Percutaneous transluminal angioplasty for intracranial atherosclerotic lesions: evolution of technique and short-term results."
J Neurosurg 1999; 91(3):415-23.

Vertebral origin angioplasty and stenting: Case series

Piotin M, Spelle L, Martin JB, Weill A, Rancurel G, Ross IB, Rufenacht DA, Chiras J. "Percutaneous transluminal angioplasty and stenting of the proximal vertebral artery for symptomatic stenosis."
AJNR Am J Neuroradiol 2000;21(4):727-31.

Malek AM, Higashida RT, Phatouros CC, Lempert TE, Meyers PM, Gress DR, Dowd CF, Halbach VV. "Treatment of posterior circulation ischemia with extracranial percutaneous balloon angioplasty and stent placement."
Stroke 1999;30(10):2073-85.

Abstracts from all of Dr. Derdeyn's publications are available at PubMed.