Emerging Therapies:
Intra-arterial Thrombolysis, Angioplasty, and Stenting

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TABLE OF CONTENTS

Introduction .................................................. 2
The Team ....................................................... 3
Feasibility: Case Illustrations .......................... 4
Thrombolysis: Rationale ................................. 5
IV Thrombolysis Trials .................................... 6
Potential Advantages to IA ............................. 7
PRO-ACT II .................................................. 8
NINDS t-PA Exclusions ................................... 9
PRO-ACT II: Results ....................................... 10
IA Fibrinolytic Agents .................................... 11
Posterior Circulation Thrombolysis .......... 12
Summary: IA Thrombolysis ........................... 13
Carotid Angioplasty and Stenting ................ 14
CAVATAS .................................................... 15
NASCET Results: 70-99% Stenosis .............. 16
ACAS Results ............................................. 17
Angioplasty and Stenting: Summary .......... 18
References ..................................................... 19

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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

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

- 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**

- 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

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

Reference:
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

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

- 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

- 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

Cross, et al. AJNR 1997, 18: 159-162
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

- 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

Reference:
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

Two year cumulative risk of ipsilateral stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical group (331 patients)</td>
<td>26%</td>
</tr>
<tr>
<td>Surgical group (328 patients)</td>
<td>9%*</td>
</tr>
</tbody>
</table>

* Includes perioperative morbidity/mortality of 5.8%

Two year cumulative risk of major or fatal stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical group (331 patients)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Surgical group (328 patients)</td>
<td>2.5%  ***</td>
</tr>
</tbody>
</table>

*** Includes perioperative morbidity/mortality of 2.1%

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

- 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**


**Evidence of an ischemic penumbra out to 24 hours**


**Thrombolysis: Clinical trials**


Possible lower rate of recanalization with iv t-PA


Basilar artery thrombolysis: Case series


Natural history of vertebrobasilar disease


Mechanical thrombolysis


Carotid endarterectomy trials

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

**Carotid angioplasty: Case series**

Circulation 1997;95:376-381


**Intracranial angioplasty: Case series**


**Vertebral origin angioplasty and stenting: Case series**


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."

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

www.strokecenter.org