

# **A Randomized Trial of Intraventricular Thrombolysis for Improved Functional Outcome in High-Grade Aneurysmal Subarachnoid Hemorrhage**

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## Background

- High-grade (Hunt-Hess IV-V) subarachnoid hemorrhage (SAH) portends poor outcome with approximately 60% mortality and major disability despite maximal treatment.
- Effective new therapy is urgently needed.

## Outcome of Patients with High-Grade (IV and V) SAH

<b>References</b>	<b>Year</b>	<b>Pt # (n)</b>	<b>Clip/Coil</b>	<b>Poor outcome*</b>
Kassell et al. J Neurosurg	1990	315	clip	69%
Roux et al. J Neurosurg	1996	159	clip	61.7%
Kremer et al. Stroke	1999	40	coil	60%
Mayfrank et al. Neurosurg Rev	2001	38	clip/coil	57.9%
Bracard et al. AJNR	2002	80	coil	37.5%
Weir et al. AJNR	2003	27	coil	70%
Laidlaw et al. Neurosurgery	2003	132	clip	60%
Suzuki et al. J Neurosurg	2006	111	coil	64.9%
Pereira et al. Neurocritical Care	2007	51	coil	43%

\* Poor outcome is defined as severe disability, persistent vegetative state or death.

## Major Predictors of Poor Outcome

- Severe intraventricular hemorrhage (IVH)
- Thick SAH on admission CT scans
- Hydrocephalus
- Vasospasm
- Delayed resorption of cisternal and ventricular blood

# Intraventricular Thrombolysis: Case Series

<b>References</b>	<b>Pt (n)</b>	<b>Thrombolysis</b>	<b>Complication</b>	<b>Poor outcome</b>
Stolke et al. Neurosurgery 1992	20	tPA 10 mg x1	None	10 %
Findlay et al. Neurosurgery 1993	10	tPA 4 mg x1-2	None	10 %
Mizoi et al, 1993	30	tPA 2mg x5	None	0 %
Usui et al 1994	60/22	Uk/tPA	5% (bleeding-tPA)	23.3/31.7 %
Moriyama et al 1995	10	Uk 60,000 U x2-4	None	10 %
Findlay et al. Neurosurgery 2004	21	tPA 4 mg x1-3	14% (bleeding)	9.5%
Varelas et al. Neurosurgery 2005	10	tPA 2-10 mg	None	10%
Verecken et al. Clin Neuro and Neurosurg 2006	18	t-PA 2-32 mg	5.6% (ventriculitis)	27.8%

# Intraventricular Thrombolysis: Randomized Trials

- **Findlay et al. Neurosurgery 1995; 37(1)168-178.**
  - Multicenter, randomized, blinded, placebo-controlled trial
  - Intraoperative single dose (10 mg) tPA (**n=51**) vs placebo (**n=49**) at 9 centers.
  - Primary endpoint: angiographic vasospasm
  - Results: similar incidence of vasospasm, but a trend of lesser degree of vasospasm in tPA group.
  - **Limitations:** small sample size, >60% pts with low grade SAH, poor endpoint.
- **Hamada et al. Stroke 2003;34:2549-2554.**
  - Randomized trial of 110 grade 1-4 patients, suitable for coil embolization.
  - Intrathecal urokinase (n=53) vs placebo (n=57) at 2 University centers.
  - Primary endpoint: symptomatic vasospasms and 6 month outcome
  - Results: reduced vasospasm (8.8% vs 30.2%) and better outcome , with permanent deficit or death at 9.4% vs 25%.
  - **Limitations:** small sample size and >60% grade 1-3 SAH patients.

## Hypothesis

Timely clearance of severe IVH and SAH with t-PA may have significantly higher outcome benefit in high-grade SAH patients.

# Study Design

- Multicenter randomized, controlled trial
- Inclusion criteria:
  - Age >18 years old;
  - Hunt and Hess grade IV and V SAH
  - Initial imaging shows severe IVH and/or thick SAH
  - Ruptured aneurysm is clipped or coiled.
- Exclusion criteria:
  - Multiple cerebral aneurysms
  - Massive intraparenchymal hemorrhage with herniation syndrome;
  - Ruptured arteriovenous malformation;
  - History of coagulopathy or bleeding disorders;
  - Pregnancy;
  - Known allergy to t-PA.

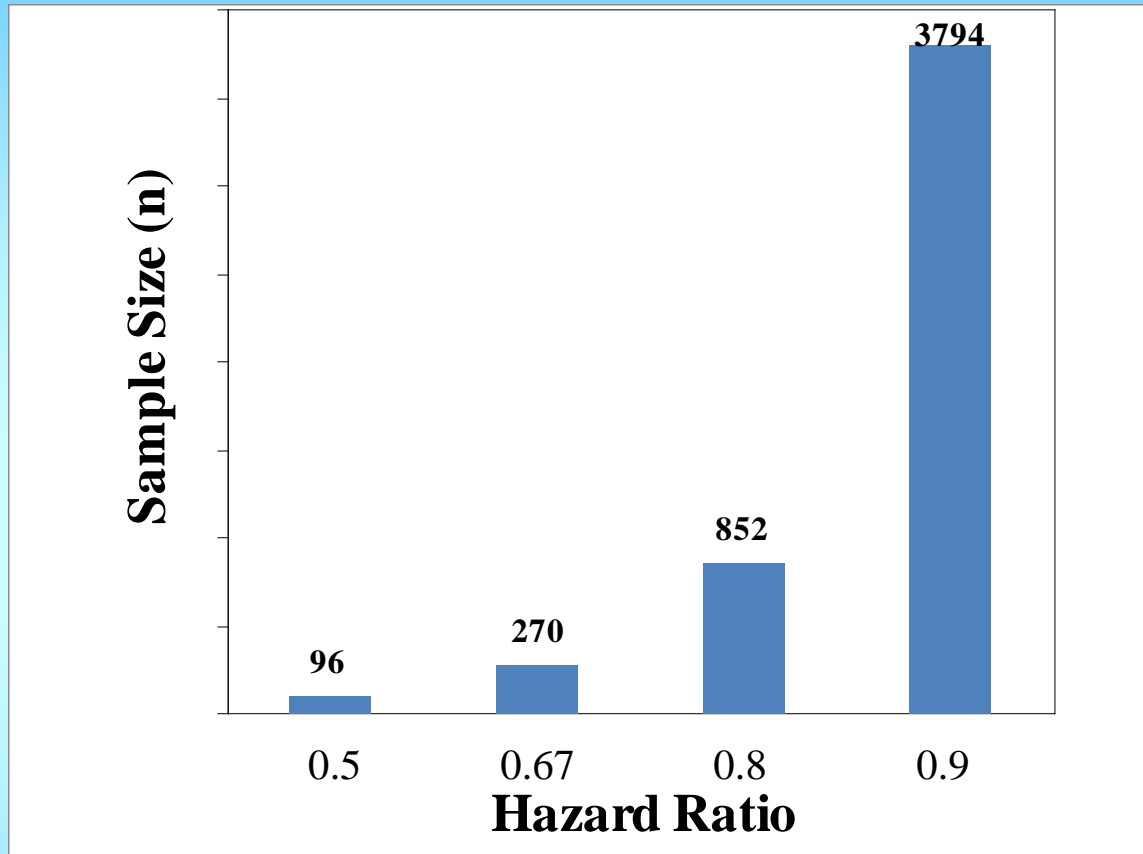
## Intervention

- Intraventricular infusion of t-PA 2 mg or placebo daily x 5 days after clipping or coiling of ruptured aneurysm.

# Main Outcome Measures

- Primary endpoint:
  - Functional outcome at 6 months. This will be assessed using modified Rankin scale.
- Secondary endpoint:
  - vasospasm-related infarction on MRI,
  - shunt-dependent hydrocephalus.

# Sample Size Calculation



Using log-rank test with an alpha of 0.05, a power of 90% and a hazard ratio of 0.67, the minimal sample size will be 270.

## Current Status

- This project is still in the idea/writing phase.
- No external funding has been applied for yet.