Cerebral Vasospasm: Current and Emerging Therapies

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Disclosures

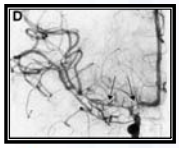
- None

Objectives

- Brief Overview
- How we got here
- Review of Trials
- "Meta-analysis"
- Future Directions

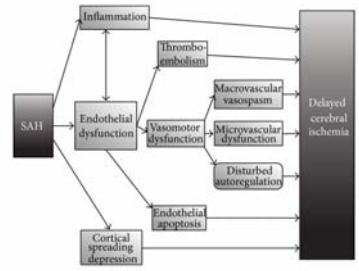
Aneurysmal SAH

- ~ 30,000 aneurysmal SAH's each year
- 20 to 40% of these patients will suffer from delayed cerebral ischemia (DCI)
  - Associated with increased morbidity and mortality
  - Cerebral vasospasm is a strong predictor of DCI
- Arterial cerebral vasospasm
  - Evident in up to 70%
  - Symptomatic in 20 to 50%



Delayed Cerebral Ischemia

- Increasing evidence suggests DCI is a multifactorial process
  - Vasospasm only one contributor



How we got here

- Cooperative Study
- Triple-H Therapy
- Nimodipine Trials
- Tirilazad
- CONSCIOUS-2 and CONSCIOUS-3 (Clazosentan)
- MASH-2 (Magnesium sulphate)
- STASH (Simvastatin)
- Future Directions

The Cooperative Study

- Randomized Controlled Trial of patients with aneurysmal subarachnoid hemorrhage
  - 1,005 SAH patients randomized to:
    - Bed Rest
    - Drug-induced hypotension
    - Carotid ligation
    - Intracranial surgery
  - Incidence of Vasospasm: 42%
    - Bed Rest: 42%
    - Drug-induced hypotension: 44%
    - Carotid ligation: 41%
    - Intracranial surgery: 39%

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Triple-H Therapy

- Induced hypertension for treatment of "ischemic symptoms" described in 1976 by Kosnik and Hunt
  - Elevated blood pressure improved neurological symptoms in 7 patients
- In 1982, Kassell et. al reported improvement in 58 patients with neurological deterioration and confirmed angiographic vasospasm
  - Improvement in 74%
  - 33% complication rate

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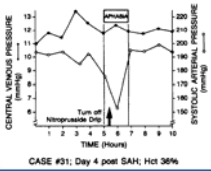
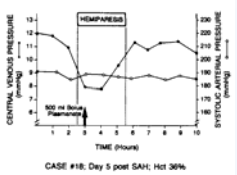
Triple-H Therapy

- Awad et. al reported on 118 SAH patients
  - "Symptomatic vasospasm" in 35.6%
  - "Good outcomes" in 34 of 42 patients with vasospasm treated with Triple-H therapy
  - 6.7% Death or Disability
  - 7% complication rate



CASE #31; Day 4 post SAH; Hct 36%



CASE #18; Day 5 post SAH; Hct 36%

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Nimodipine (Only FDA Approved Therapy)

- In good grade SAH patients (Allen GS, et al. NEJM, 1983)
  - Diminished neurological deficits (1/56) vs. placebo (8/60) attributed to vasospasm
- In poor-grade aneurysm (Petruk KC, et al. JNS, 1988)
  - Better outcome at 3 months (29.2% vs. 9.8%)
- British aneurysm nimodipine trial (Pickard et al. BMJ 1989)
  - 554 patients nimodipine vs. placebo
  - Poor outcome 20% vs. 33% placebo (Risk Reduction of 40%)
  - 34% angio-negative SAH
  - 58% did not undergo treatment of an aneurysm

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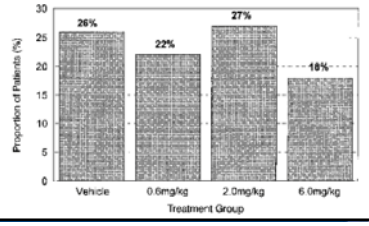
Tirilazad

- An aminosteroid and a potent inhibitor of oxygen radical-induced lipid peroxidation
- Tirilazad (Europe, Australia, and New Zealand)
  - Kassell et al (JNS 1996)
  - 1,015 patients in RCT of multi-dose tirilazad vs. placebo (+/- nimodipine, +/- prophylactic Triple-H)
  - 28% poor outcome in high-dose vs. 34% placebo



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Tirilazad

- Tirilazad (North American Cooperative)
  - Haley et al (JNS 1997)
  - 897 patients in RCT of multi-dose tirilazad vs. placebo (+nimodipine, +/- prophylactic Triple-H)
  - No difference in 3 month outcome (placebo 27% poor vs. 30% in treatment arm)

Incidence of symptomatic vasospasm in randomized patients with aneurysmal SAH

Condition & Therapy	Vehicle-Treated Group (300 patients)	Tirilazad-Treated Groups: 2 mg/kg/day (298 patients)	Tirilazad-Treated Groups: 6 mg/kg/day (299 patients)
symptomatic vasospasm (%)	100 (33)	88 (30)	98 (33)
cerebral infarction at 14 days (%)	81 (27)	102 (34)	101 (34)
neurological worsening (%)	145 (48)	164 (55)	160 (54)
due to vasospasm (%)	71 (24)	60 (20)	80 (27)
therapeutic hypervolemia, hypertension, & hemodilution (%)	89 (30)	74 (25)	86 (29)
cerebral angioplasty (%)	31 (10)	19 (6)	32 (11)

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Endothelin Receptor Antagonists

- ET-1 overproduction is a leading theory for pathogenesis of vasospasm
- Clazosentan —> endothelin receptor agonist
  - CONSCIOUS-1 (Phase II Trial)
    - clazosentan reduced the frequency of vasospasm in a dose-dependent fashion
    - highest dose was associated with 65% relative risk reduction in vasospasm

CONSCIOUS-II (Phase 3 RCT)

- 1,157 SAH patients undergoing clipping

Table 1. CONSCIOUS-2: Primary Endpoint

Endpoint	Placebo	Clazosentan	Relative Risk Reduction (95% CI), %	*P* Value
Death or vasospasm-related morbidity, %	25.3	21.1	17 (−4 to 33)	.1037

CI = confidence interval

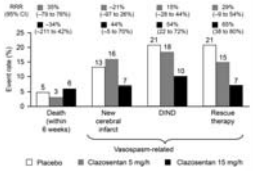
Table 2. CONSCIOUS-2: Patients With Poor Outcome (GOSE Score ≤4) by Treatment

Endpoint	Placebo	Clazosentan	Relative Risk Reduction (95% CI)	*P* Value
GOSE score <4, %	24.8	29.3	-18 (-45 to 4)	.1048

CI = confidence interval; GOSE = Glasgow Outcome Scale

CONSCIOUS-III (Phase 3 RCT)

- 571 SAH patients undergoing coiling
  - Halted prematurely following completion of CONSCIOUS-II
    - Primary Outcome



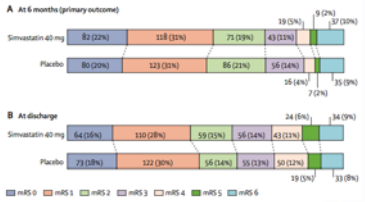
    - Secondary Outcome:
      - No difference in poor outcome 24% placebo vs. 25% and 28% in treated groups

MASH-2: Magnesium (Phase III RCT)

- Neuroprotective and vasodilatory properties
- Early studies suggested possible benefit in preventing ischemic damage
- Phase 3 RCTs: MASH-2 (1204 patients)
  - IV magnesium did NOT increase the probability of good outcome or decrease risks for cerebral infarction, radiographic vasospasm or mortality
- No evidence to support use

STASH: Simvastatin (Phase III RCT)

- Beneficial effects on endothelial inflammation, oxidative stress, and inhibition of platelet adhesion and aggregation
- 803 SAH patients randomized



- No difference

"Meta-analysis"

- Compare outcomes from Nimodipine Trial to other SAH trials (ISAT and BRAT)

Nimodipine Treated Patients			
Trial	Total Patients	Total Poor Outcome	Proportion w/ Poor Outcome
British Nimodipine Trial	278	55	20%
ISAT - surgical	1063	392	37%
BRAT - surgical	205	69	34%
Non-nimodipine Total	1268	461	36%

- 17% reduction in poor outcome in the British Nimodipine Trial compared to ISAT and BRAT
  - 95% CI (11% to 22%) $p < 0.0001$
- A patient in ISAT or BRAT was 2.3 times more likely to have a poor outcome than a patient treated in the British Nimodipine Trial
  - 95% CI (1.7 to 3.2) $p < 0.0001$

What gives?

- Peculiar things about Nimodipine and its trials
  - No other Ca2+ channel blocker has been effective
  - We don't know why it works
    - No effect on angiographic vasospasm
  - Original trials no hypotension
    - Nimodipine discontinued in 1% for hypotension
    - Today up to 30% will have it stopped
  - No study has come close to repeating the effect size seen in the British Nimodipine Trial
    - 34% of patients would be excluded in current trials

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Future Directions

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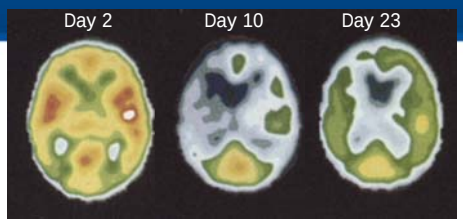
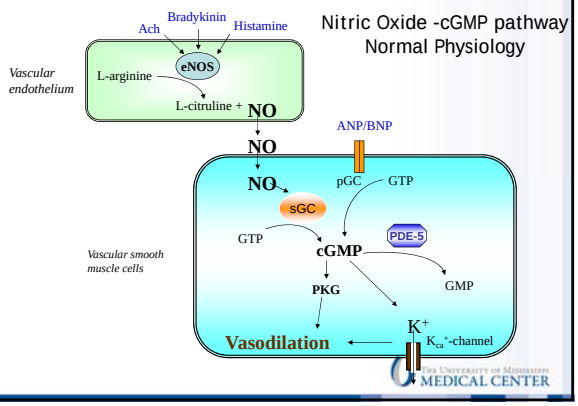
A Phase I Clinical Trial

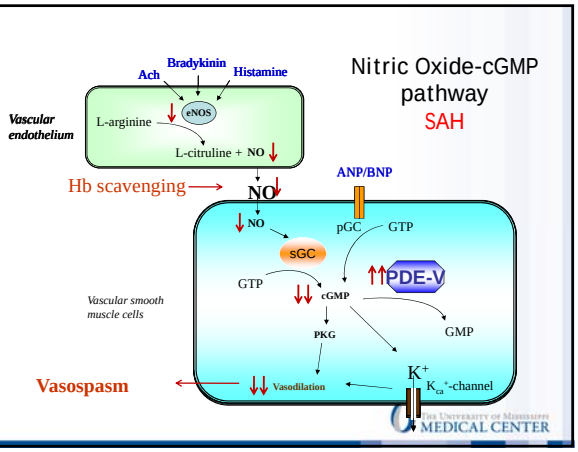
of Sildenafil for the Treatment of Cerebral Vasospasm Following Subarachnoid Hemorrhage



Sildenafil: A Potential Therapy

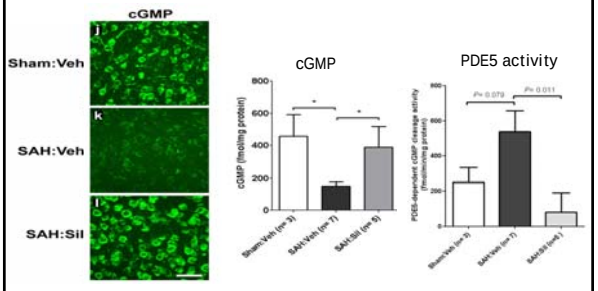
- Phosphodiesterase V inhibition
  - In animal models of SAH
    - Reduces larger artery vasospasm
    - Improves neurological outcomes
    - Restores impaired autoregulatory mechanisms
  - In non-SAH humans
    - Augments autoregulatory mechanisms
  - In SAH humans
    - Evidence of improved vasospasm based on TCD





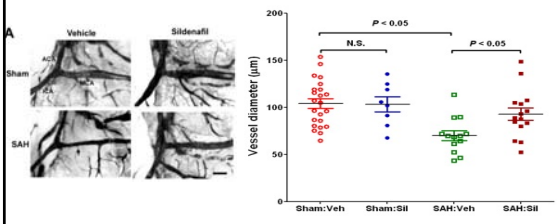
Animal Results

Sildenafil decreases PDE5 activity and cGMP levels after SAH



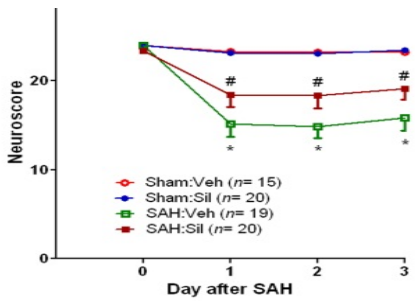
Animal Results

Sildenafil reduces SAH-induced vasospasm



Animal Results

Sildenafil reduces SAH-induced neuro deficits



Study Design

- A prospective non-randomized Phase I trial investigating sildenafil in a series of controlled dose escalation studies with

Specific Aims:

1. Determine the safety of intravenous sildenafil in SAH patients
2. Assess its ability to reverse angiographic vasospasm
3. Study the effect of intravenous sildenafil on CBF

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Methods: Protocol

Two phase protocol

- Phase I – 6 patients
  - Single 10mg low dose
  - Angiography or PET
- Interim safety analysis
- Phase II – 6 patients
  - Two 30mg high doses
  - Angiography AND PET

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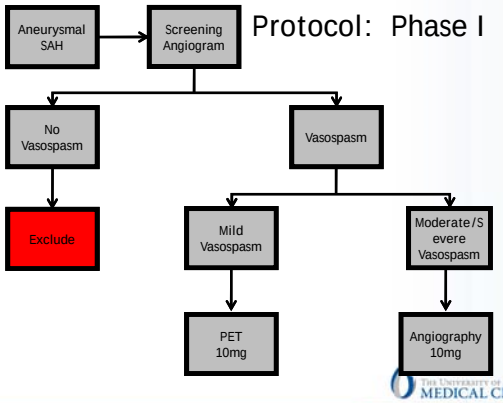
Protocol: Phase I



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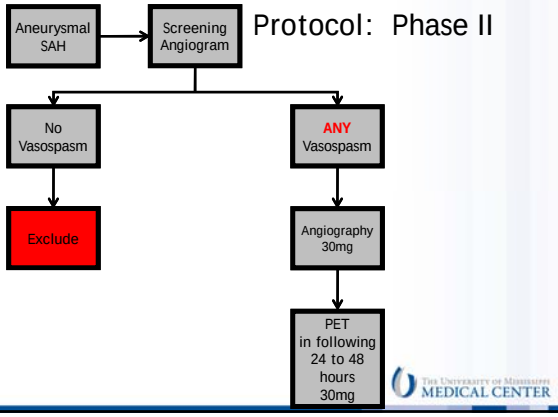
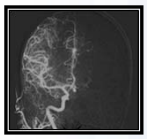
Protocol: Phase II



Methods: Angiography and PET

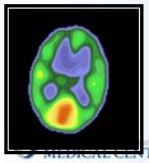
Following screening angiogram

- Receive sildenafil dose
  - 30 min wait time
- Repeat diagnostic angiogram



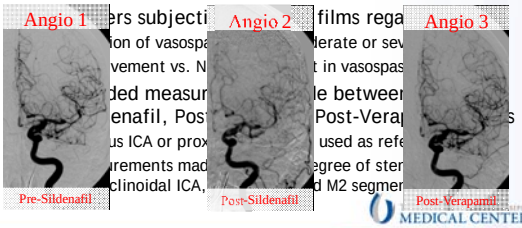
PET studies 24 to 48 hours following first sildenafil dose

- Baseline PET: resting CBF
- Receive sildenafil dose
  - 30 min wait time
- Repeat PET: resting CBF



Analysis: Angiography

- Blinded reviewers labeled films as
  - Pre-Sildenafil
  - Post-Sildenafil
  - Post-Verapamil (when available)



Results

- 23 patients enrolled
- 12 patients completed study
  - 6 patients received 10mg dose
    - 5 Angiography
    - 1 PET
  - 6 patients received 30mg dose
- PET unavailable for 4 patients
- 2 patients did not undergo 7-day angio
- 5 patients no vasospasm

Results: Demographics

Age	55.5 (38 to 83)
Gender	
Male	6 (50%)
Female	6 (50%)
Hunt & Hess Grade	
II	3 (25%)
III	4 (33%)
IV	3 (25%)
V	2 (17%)
Treatment	
Clip	5 (42%)
Coil	7 (58%)

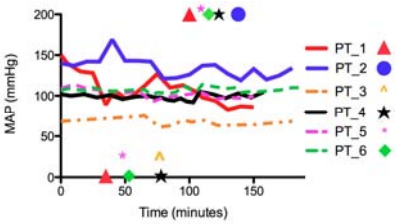
modified Fisher Grade	
I	1 (8%)
II	0 (0%)
III	5 (42%)
IV	6 (50%)
Aneurysm Location	
ACA	1 (8%)
Acomm	5 (42%)
MCA	1 (8%)
PICA	1 (8%)
Pcomm	4 (33%)

Results: Safety

- No adverse events
- Stable neurological exams following infusion
  - 1 patient with improvement (resolution of pronator drift)
- No adverse effect upon
  - Heart rate
  - Oxygen saturation
  - Intracranial pressure

Results: Blood Pressure

Phase I: 10mg Sildenafil Dose



ID	Percent Drop (%)	Return Time (min)
1	35	40
2	16	30
3	13	15
4	8	0
5	16	10
6	6	0

Average decline in MAP: 16%
Average time to return: 16 mins

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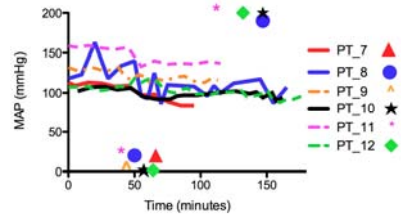
Results: Blood Pressure

Phase II: 30mg Sildenafil Dose, Angiography



ID	Percent Drop (%)	Return Time (min)
7	21	50
8	34	75
9	17	20
10	12	15
11	15	NR
12	12	5

Average decline in MAP: 19%
Average time to return: 33 mins

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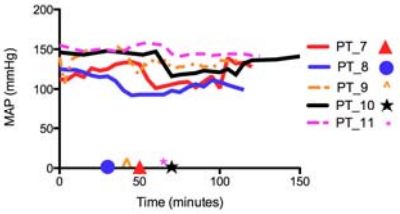
Results: Blood Pressure

Phase II: 30mg Sildenafil Dose, PET



ID	Percent Drop (%)	Return Time (min)
7	18	35
8	24	55
9	16	4
10	19	40
11	10	0

Average decline in MAP: 17%
Average time to return: 27 mins

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Results: Angiographic Response

- 7 of 11 (64%) patients with identified improvement (none worsened)

10mg Sildenafil Dose

ID	Vasospasm Severity	Improve Post-Sildenafil	Maximum Dilatation (mm)
1	Severe	Yes	1.25
2	Mod	Yes	1.25
4	Mod	No	NA
5	Mod	No	NA
6	Mod	Yes	0.83

3 of 5 (60%) improved

30mg Sildenafil Dose

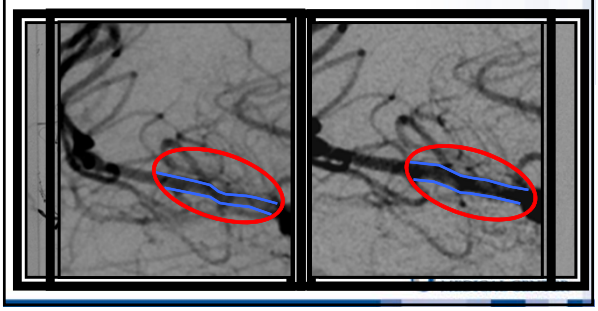
ID	Vasospasm Severity	Improve Post-Sildenafil	Maximum Dilatation (mm)
7	Mod	No	NA
8	Severe	Yes	1.25
9	Mod	No	NA
10	Severe	Yes	2.1
11	Severe	Yes	1.25
12	Severe	Yes	0.6

4 of 6 (67%) improved

Average dilatation (all patients): 0.8 mm
Average dilatation (responders): 1.25 mm

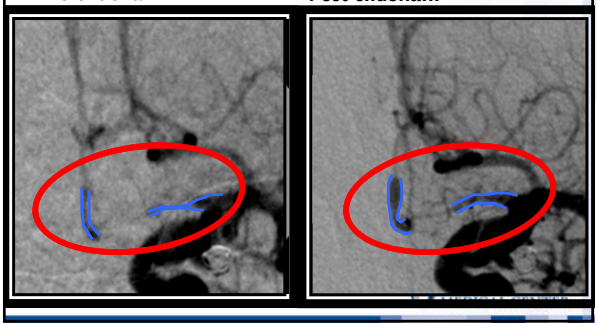
Results: Angiographic Response

Pre-sildenafil **Post-sildenafil**



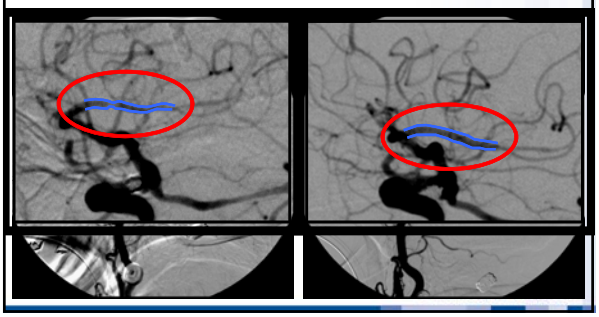
Results: Angiographic Response

Pre-sildenafil **Post-sildenafil**



Results: Angiographic Response

Pre-sildenafil **Post-sildenafil**



Conclusions

Intravenous sildenafil to treat post-SAH cerebral vasospasm is:

- Safe
  - No adverse events
  - Acceptable blood pressure profile
    - Transient 16-19% decline in MAP
- Evidence of a positive angiographic response in select patients (64%)

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Future Directions

- Pharmacokinetic/Pharamacodynamic Translational Study
  - Compare pharmacokinetic differences between oral and intravenous sildenafil in SAH patients
  - Determine if oral sildenafil has a more favorable hemodyanmic profile
  - Assess the effects of sildenafil on:
    - Cerebral vasospasm measured by transcranial Doppler
    - Cerebral autoregulation

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Questions?

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