Elucidation of Nitric Oxide (NO) Role in Vasospasm and Cortical Spreading Ischemia in a Primate Model of Aneurysmal Subarachnoid Hemorrhage

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SAH induced cerebral vasospasm occurs between day 4-9

20–30% experience delayed ischemic neurological deficits (DIND)

50% of these patients suffer severe permanent neurological dysfunction or death
Delayed ischemic neurologic deficits (DIND) after SAH vs angiography

- Cause of disability in 6.3% of SAH pts
- Cause of death in 7.2%
- Time course of DIND similar to angiographically visible vasospasm:
  - However, angiographic vasospasm has only a positive predictive value for DIND of <50%

- Cerebral vasospasm ≠ delayed ischemic neurological deficit (DIND)
Concepts of treatment

- Enhance Perfusion
- Reversal of Arterial Narrowing
- Prevention of Arterial Narrowing
- Ischemic Protection & Rescue

1. HHHH Therapy
2. Enhance availability of nitric oxide (NO)
Baseline angiogram on day 0 prior to SAH.

SBP = 81 mmHg
DBP = 57 mmHg
MAP = 65 mmHg
pCO2 = 53.6 mmHg

Follow-up angiogram on day 5 after SAH prior to initiation of NE infusion.

SBP = 83 mmHg
DBP = 58 mmHg
MAP = 67 mmHg
pCO2 = 45.6 mmHg
(Width = 57.3 % Baseline)

Follow up angiogram on day 5 after SAH during infusion of NE.

SBP = 200 mmHg
DBP = 129 mmHg
MAP = 158 mmHg
pCO2 = 45.6 mmHg
(Width = 160 % Baseline)
Changes of Basilar Artery Diameter

Changes of basilar artery diameter in % of control

- Control
- No SAH NE
- SAH
- SAH NE

* p < 0.05
Enhanced availability of nitric oxide (NO)

- Decreased availability of nitric oxide (NO) in the arterial walls of the circle of Willis has been linked to development of delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) in both clinical and experimental settings (Pluta RM, Neurol Res 2006 Oct;28:730-737).

- Main problem: local delivery of high concentrations of NO or NO donors.

- Recently, it was reported that sodium nitrite is a stable reservoir of NO and when given intravenously, can prevent arteriographic vasospasm in a primate model of aSAH.
  

- Additionally we could demonstrate that intrathecal continuous administration of nitroglycerin as a NO donor prevents CVS in a rabbit SAH model.
• Prophylactic continuous intrathecal administration of nitroglycerine prevents vasospasm of the basilar artery in the rabbit SAH model

• No toxic effects could be demonstrated in this study
The Clazosentan study

- Clazosentan reduces incidence of angiographic vasospasm
- No improvement in clinical outcome at 3 months (DIND, mortality)

COSBID

• The Co-Operative Study on Brain Injury Depolarizations (COSBID)

• a prospective clinical multicenter study

• demonstrated delayed clusters of cortical spreading depolarization (CSD) in SAH patients

• In many patients, clusters of prolonged depolarization occurred

• These patients developed ischemic infarcts in the recording area, indicating that CSDs may be linked to DINDs

New Concept

• delayed cerebral vasospasm is not the only factor responsible for poor outcome after successful treatment of aSAH

• rather, there are two important factors responsible for the clinical outcome:

  (1) delayed spasm of large cerebral arteries
  (2) spreading depolarizations producing cortical infarcts
Primate model for cortical ischemia

- Day 14 post SAH
- cortical laminar necrosis
- no territorial infarct
- no white matter changes

Schatlo et al, *abstract award: AANS 2008*
Cortical Spreading Depression

1. Depolarization
2. Neuronal metabolic suppression
3. Disturbance of neuronal microenvironment, $K^+\uparrow$
4. Need of ATPase to pump $K^+$ back into cell
5. Increased metabolic demand
6. Reactive hyperaemia with increased demand of Nitric Oxide

Goals

• we will employ a primate model of aSAH that has been used in the Vascular Laboratory of the Surgical Neurology Branch, NINDS for several years to study delayed cerebral vasospasm


• our hypothesis is that oral administration of sodium nitrite, especially in the presence of ascorbic acid will prevent development of delayed cerebral vasospasm and cortical infarcts by preventing cortical spreading ischemia

• to establish the most effective oral sodium nitrite and/or sodium nitrite/ascorbic acid dose that does not cause a hypotensive response or other side effects (methemoglobinemia) but which prevents vasospasm and/or cortical infarcts

• the ultimate goal: is to prove that a primate model of aSAH is adequate to examine the therapeutic effect of drugs which affect development of delayed cerebral vasospasm and delayed ischemic neurological deficits
Thank You
AND

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