Safety and Efficacy of Prophylactic Intrathecal Sodium Nitroprusside for the Prevention of Delayed Cerebral Ischemia

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IRB Protocol

A. Study Purpose and Rationale

The purpose of this study is to investigate a novel treatment for the prevention of cerebral vasospasm and associated neurological morbidity following subarachnoid hemorrhage. After aneurysmal subarachnoid hemorrhage (SAH), 70% of patients will experience angiographic cerebral vasospasm, or constriction of major cerebral arteries, and nearly 40% of these patients will suffer from clinically observable neurological deficits[1]. Several modalities, including HTN, hemodilution, hyperdynamic cardiac states, and nimodipine, currently exist to treat/prevent cerebral vasospasm. However, none of these have been shown to be highly efficacious.

Despite the quantum leap in rational therapies in the past 40 years, the direct mechanism for vasospasm. following SAH remains unknown. However, recent work has implicated nitric oxide (NO) as a major factor in the etiology of cerebral vasospasm., specifically due to a deficiency in its vasodilatory influence1[2-3] One of the predicting factors for vasospasm following SAH is the size of the resultant hemorrhage/blood clot[4]. This correlation may result from a decrease in baseline NO acting on cerebral vasculature. Oxyhemoglobin present in the accumulating blood following SAH avidly binds NO thereby mitigating its vasodilatory action [5-6]. Additionally, the liberation of superoxide radicals as seen in SAH has been suggested to ftu-ther inactivate NO. [13] This evidence suggests that cerebral vasospasm. in the setting of SAH might be partly due to misregulation of cerebral vasomotor tone secondary to a functional deficiency of NO.

Sodium nitroprusside (SNP), an NO donor, has been shown to elicit vasodilation through the same guanylate cyclase/cGMP dependent mechanism that endogenous NO is believed to function. Through this pathway it has been demonstrated to reverse the effects of ET-1 induced cerebral vasoconstriction[4]. Considering the mechanistic advantages of SNP recent clinical studies have focused on using this agent intrathecally to reverse symptomatic spasm [8-9]. Despite these initial studies there has been little further experience establishing the safety and efficacy of this treatment modality.

Between 50 to 75% of patients who survive a poor grade SAH will suffer from ischemia due to vasospasm. during the spasm perdiod, days 4-12. As SNP appears to reverse cerebral vasoconstriction, prophylactic treatment with SNP during this window of highest vasospasm risk might serve to decrease the incidence of this delayed cerebral ischemia. This prospective study seeks to provide more extensive data on the safety and efficacy of intrathecal SNP treatment for prophylaxis of cerebral vasospasm secondary to poor grade aneurysmal SAH.

B. Study Design and Statistical Analysis

This is a single center, prospective, randomized, blinded, placebo-controlled, clinical trial in aneurysmal SAH patients.

Experimental and Control Groups: 44 (22 in each arm) adult patients with severe subarachnoid hemorrhage (SAH), Hunt-Hess grade 3-5, secondary to a ruptured cerebral aneurysm will be enrolled. The patients will be stratified into the appropriate Hunt-Hess grades and randomized within those

classifications to either receive SNP or placebo. This will ensure that within each grade there is an equal number of treatment and controls allowing for subgroup analyses. The research pharmacist will assign the groups. The neurosurgeon and neurologist will at no time know the assignment of the patients The patient's assigned treatment will be revealed for any of the following reasons: hemodynamic instability defined to be an inablility to maintain the systolic blood pressure within 25% of the patient's normal values for longer than 15 minutes, cardiac ischemia as determined by EKG changes, or seizure. Normal blood pressure will be defined as either the latest preoperative value or the value from the admission unit.

a. Study Size

Since we intend to show SNP to be safe by not causing more than a 20 min Hg drop in systolic blood pressure, and the standard deviation of SBP is approximately 20 mm Hg, we will need 22 patients in each arm to achieve $\alpha = 0.05$, $\beta = 0.90$. This study will not be powered specifically to demonstrate efficacy.

b. Statistical Analysis

The demographic data of the patients including age, race, sex, description of aneurysm fixation, and Hunt-Hess grade at presentation will be summarized. Overall control and treatment groups and subgroups (within grades) will be compared. Qualitative variables will be compared by Chi-square analysis. Quantitative variables will be compared by analysis of variance.

C. Study Procedures

a. **Medical management of acute subarachonoid hemorrhage**

All patients being admitted to the hospital for SAH (Hunt-Hess grade 3-5) will be given standard of care for the medical/surgical management of acute subarachnoid hemorrhage as dictated at the Neurological Institute at New York Presbyterian Hospital.

Pre-operative management: Preoperative management will be based on the standard of care for aSAH patients as dictated by the Neurological Institute of New York. Patients will receive an external ventricular drain (EVD) as indicated for treatment of symptomatic hydrocephalus. Patients will be treated with the appropriate regimens of anti-epileptic and calcium channel blocking medications. Cerebral angioraphy will be performed for clinical assessment of treatment options (surgical clipping or embolization). A multidisciplinary team at CPMC will make the decision regarding the most appropriate intervention

Post-operative management: Central venous lines will be inserted on all patients in the OR. In addition, Licox probes will be inserted in the OR to continuously monitor cerebral tissue oxygen tension (Pti02). Patients will maintained in a euvolumic state. In the NICU, patients will receive hourly neurological exams. In cases where the glascow coma score drops two points or more, hypertensive, hyperdynamic, hernodilution therapy will begin and a CT scan will be performed to rule out infarction or increased bleeding. If no improvement is seen within two hours then angiography will be performed and interventions to follow will be dictated by standard of care.

b. **Administration of experimental medication**

At post SAH day 3 (no more than 72 hrs. post event), the experimental treatment will begin to be ended on SAH day 12. A closed infusion/transduction system will be attached to the EVD for the administration of the study drug, sodium nitroprusside (SNP). The EVD will remain open at clinically indicated levels except during the infasion of SNP or control solutions SNP will be diluted to 4 mg/niL in artificial CSF and infused through the EVD of in consecutive 8 hour intervals (total of 3 treatments per 24 hours). **The volume of SNP/aCSF solution added during each treatment will be calculated to yield a total of 0.5 mg SNP/kg/day for each patient (-30 mg SNP/24 hours).** Control patients will be administered matching volumes of artificial CSF solution only. Vital signs and Licox measurements will be continuously monitored during and after the treatments.

c. **CSF and serum testing**

CSF will be withdrawn by proper sterile technique through the EVD for management of intracranial pressure. CSF samples will be stored and analyzed for thiocyanate levels. Blood samples (5 mL) will be drawn from existing intra-arterial lines or by venous puncture during the second and seventh daily treatment. These samples will be analyzed for thiocyanate levels by an independent observer not associated with the study.

d. **Outcome measures**

The primary outcome measures will be in two different categories:

i. **Safety**

Safety in prophylactic SNP administration to SAH patients is the primary outcome of this study.. These measures will include the patients' general physiological stability and specific potential complications due to treatment. The stability of patients' vital signs including blood pressure, heart rate, temperature, and ICP will be evaluated before, during, and after treatment. Stability of vitals due of treatment group will be determined relative to controls. A systolic blood pressure decrease of greater than 20 min Hg will characterize the patient as having hypotension secondary to SNP. Deviations greater than 25% in any other measure that is consistent between both groups will be further analyzed for potential threat to patients. Specific complications that will be evaluated will be cyanate toxicity, CNS and infectious complications. Cyanate levels in CSF (both from EVD and spinal tap) and serum will be measured on the second and seventh days of treatment. Concentrations of cyanate in serum greater than 0.5 to 1.0 ~Lg/ml are known to be toxic (causing tachycardia and flushing)10.

As it is hypothesized that SNP treatment will increase cerebral blood flow, post-study CT scans will be performed to evaluate for increased hemorrhage complications. Finally, while the EVD infusion apparatus and proper sterile technique should minimize risk of infections, patients will be monitored for potential infectious complications.

ii. **Efficacy**

Although this pilot study is designed to assess the safety of SNP administration and is not powered for efficacy determination, it is hoped that the data will provide preliminary indications of treatment benefit. NO mediated vasodilation of cerebral vessels due to SNP infusion should result in an increase in cerebral blood flow' a decrease in the flow velocity and an increase in the oxygenation of the brain tissue. LICOX probes will provide continuous polarographic brain tissue oxygen (Pti02) and regional cerebral blood flow readings pre, during, and post treatment to evaluate the effect of SNP on these specific biological, parameters. In addition, transcranial doppler (TCD) exams will be administered daily to measure the degree ~f vasoconstriction, identified as an increase in flow velocity. TCD values will allow for determination of the risk of vasospasm. Sekhar et al. has shown that TCD values demonstrating middle cerebral artery blood flow >200 cm/sec suggests the diagnosis of vasospasm. Risk for vasospasm for those values below 120 cm/sec is comparatively little. There are no known risks associated with TCD ultrasonography. Angiograms will be performed as clinically indicated or post study (post SAH day 10) to obtain a radiographic determination of cerebral vessel caliber and clinically unobserved vasospasm. Appropriate CSF and blood samples will be collected for future analysis in studies investigating the role of cytokines and other biological molecules in stroke and cerebral ischemia. In addition to measurements of specific biological parameters, more general efficacy outcomes will also be measured. Glascow coma scores at enrollment and at end of study (post SAH day 14) will be compared for overall neurological improvement.

This study is expected to last for one year with each patient participating for approximately two weeks.

D. Study Drug

Sodium nitroprusside (SNP), a nitric oxide (NO) donor, is a FDA approved drug for systemic infusion to treat hypertension. The intrathecal injection of SNP through an EVD for the prophylactic treatment of vasospasm. in SAH patients is a non-standard route of administration for an off-label

indication. The rationale behind this deviation from standard use of SNP is that recent work suggests that vasospasm secondary to SAH may result from a deficiency in NO activity in cerebral vessels [3-8].

Previous clinical studies suggest that intrathecal SNP treatment reverses cerebral vasospasm following SAH and has a minimum of complications[6-8] This study will examine the safety of prophylactic administration of SNP in poor grade SAH patients during the risk period for vasospasm. (days 3 to 12). The dosing of SNP will follow the protocol used in previous studies: three 2-3 mL infusions of a 4 mg/mL solution of SNP in consecutive 8 hour intervals yielding a total of 0.5 of SNP mg/kg per 24 hours. However, a few changes will be made so as to reduce potential risks associated with the treatment. First, SNP will be diluted in artificial CSF (aCSF) (composition as dictated by research pharmacy) rather that CSF withdrawn from patient through EVD prior to infusion. Second, a closed infusion/transduction system will be attached to the EVD for the administration of SNP/aCSF. These two changes will reduce the risk of CNS infection due to contamination of CSF or EVD. Finally, the SNP treatments will continue during post SAH days 3 to 12 rather than for one day after vasospasm has occurred.

Known potential side effects of SNP treatment are nausea, hypotension and cyanate toxicity.

E. Medical Devices

A closed infusion/transduction system will be attached to the EVD for the infusion of the SNP/control solution. This apparatus merely allows for infusion through the EVD during short intervals of time and minimizes risk of infection associated with open drain. When treatments are not taking place the system will allow for the drain to be opened to the clinically indicated level for CSF removal and ICP regulation.

F. Study Questionnaires

Study questionnaires will not be used.

G. Description of Study Subjects and Method of Recruitment

The study subjects must meet the following criteria:

a. Inclusion criteria

- Age 18 years to 65, male or female.
- Post SAH day 2. Patients must be enrolled and started on treatment less than 72 hours after SAH.
- External ventricular drain (EVD) placement as clinically indicated for symptomatic hydrocephalus. The decision to place the EVD will be made prior to and independent of the decision to enroll.
- CT scan prior to enrollment to locate ventricular catheter and ensure that it is properly place in lateral or third Ventricles.
- Hunt and Hess grade 3-5, and Fisher scale grade 3 or higher upon placement of the EVD.
- Licox monitor placement prior to study enrollment as clinically indicated for continuous observation of cerebral tissue oxygen tension..
- Written and informed consent obtained directly from patient's healthcare proxy

b. Exclusion criteria

- Untreated ruptured aneurysm
- Intracranial pressure not reducible below 20 cm H20 by medical therapy.
- History of permanent neurologic impairment, including known seizure disorder.
- Renal or hepatic impairment.

- Pregnancy
- Medical contraindication to SNP treatment. (state these)
- Medical complication: Acute MI - Troponin I >10; pulmonary disease or complication preventing adequate systemic oxygenation (02 sat < 95%)
- Diffuse cerebral edema
- Intracerebral hemorrhage.

H. Recruitment of Subjects

Patients will be recruited by an attending Neurologist or Neurological Surgeon upon admission to the hospital. The investigator will explain the risks and benefits of participation in the study in detail to the patient. A written consent form will be signed by the patient's next of kin or healthcare proxy prior to their enrollment in the study. (Our inclusion criteria (grade 3-5 SAH) eliminate patients with the capacity to give consent on their own behalf.)

I. Confidentiality of Study Data

All data will be kept confidential with a unique study number. Identifying data will be recorded at the local site for follow-up purposes, but will not be entered into the study charts. Charts will be maintained in a locked office of the Department of Neurological Surgery, which is accessible to authorized personnel only.

J. Potential Conflict of Interest

No investigator has a proprietary interest in any drug, device or procedure under investigation.

K. Location of Study

The study will be conducted at the Columbia Presbyterian Medical Center (Milstein Hospital Building).

L. Potential Risks

Two potential risks associated with the use of SNP are cyanate toxicity and hypotension due to systemic vasodilation. Previous studies have shown that intrathecal administration of SNP in comparable doses results in no detectable serum thiocyanate during or after treatment.[7-9] This study will measure serum thiocyanate levels as well as thiocyanate levels in CSF from EVD to assess this risk.

Blood pressure will be continuously monitored during treatment to control for potential hypotension due to treatment. The injection of SNP into the ventricular system and the extremely short half-life of NO decrease the likelihood of systemic vasodilation and resultant hypotension. If hypotension occurs, standard treatment will be initiated by the ICU staff.

M. Potential Benefits

This is primarily a study assessing the safety of prophylactic SNP treatment in SAH patients. However, there may be potential benefit to patients receiving treatment if SNP increases the vasodilatory tone of the cerebral vasculature during the vasospasm period thereby decreasing the risk of delayed neurological deficit.

N. Alternative Therapies

Standard of care will be adhered to in this trial. The alternative is simply to not participate in the trial (not be randomized to receive nitroprusside or control).

O. Compensation to Subjects

No monetary compensation will be given to participants.

P. Cost to Subjects

There is no additional cost to subjects.

Q. Minors as Research Subjects

No one under the age of 18 will be enrolled in this study.

R. Radiation or Radioactive Substances

Not applicable

S. Consent Form For A Research Study

Pending

T. References

1. Biller, J., Godersky, J.C., Adams, H.P. Jr. Management of aneurysmal subarachnoid hemorrhage. **Stroke** 19:1300-1305, 1988.
2. Fujiwara, S., Kassell, N.F., Sasaki, T., Nakagomi, T., Lehman, R.M. Selective hemoglobin inhibition of endothelium-dependent vasodilation of rabbit basilar artery. **I Neurosurg.** 1986;64:445-452.
3. Hongo, K., Kassell, N.F., Nakagomi T., Sasaki, T., Tsukahara, T., Ogawa, H., Vollmer, D., Lehman, R. Subarachnoidhemorrha& inhibition of endothelium-derived relaxing factor in rabbit basilar artery. J. Neurosurg. 1988;69:247-253.
4. Thomas, J. E., Nemirovsky A., et al. Rapid reversal of endothelin-I -induced cerebral vasoconstriction by intrathecal administration of nitric oxide donors. Neurosurgery 40(6):1245-9, 1997.
5. Kanamaru, K., Waga, S., et al. Enodthelium-dependent relaxation of canine basilar arteries, part 2: inhibition by hemoglobin and cerebrospinal fluid from patients with aneurismal subarachnoid hemorrhage. **Stroke.** 18: 938-43, 1987.
6. Egeman, N., Turker, R. K., et al. The effect of intrathecal sodium nitroprusside on severe chronic vasospasm. Neurol Res. 15: 310-15, 1993
7. Vajkoczy, P., Hubner, U., et al. Intrathecal Sodium Nitroprusside Improves Cerebral Blood Flow and Oxygenation in Refractory Cerebral Vasospasm and Ischemia in Humans. **Stroke** 31(5): 1194-b, 2000.
8. Thomas, J. E., Rosenwasser, R. H., et al. Safety of Intrathecal Sodium Nitroprusside for the Treatment and Prevention of Refractory Cerebral Vasospasm and Ischemia in Humans. **Stroke** 30:1409-1416, 1999.

9. Thomas, J. E, Rosenwasser, R.H. Reversal of Severe Cerebral Vasospasm in Three Patients after Aneurysmal Subarachnoid Hemorrhage: Initial Observations Regarding the Use of Intraventricular Sodium Nitroprusside in Humans. **Neurosurgery** 44(l): 48-58, 1999.
10. Hall AH, Rumack BH. Clinical toxicology of cyanide. **Ann Emerg Med** 1986 Sep;15(9):1067-74.
11. Sekhar LN, Wechsler LR, Yonas H, Luyckx K, Obrist W. Value of transcranial Doppler examination in the diagnosis of cerebral vasospasm. after subarachnoid hemorrhage. **Neurosurgery** 1988 May;22(5):813-21.
12. Vollmer, D.G., Hongo, K., Ogawa, H., Tsukahara, T., Kassel, N. A study of the effectiveness of the iron-chelating agent deferoxamine as vasospasm prophylaxis in a rabbit model of subarachnoid hemorrhage. Neurosurgery 28:27-32, 1991.