

A Prospective, Randomized, Single-Surgeon Trial of Fenestration of the Lamina Terminalis

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A. Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) following ruptured intracranial aneurysm affects approximately 25,000 to 30,000 people each year. Despite advances in early diagnosis and management, aSAH remains a frequent cause of death and disability. A common complication of this disease is hydrocephalus, a condition where the fluid surrounding the brain does not drain properly, causing an increase in pressure. In order to prevent damage to the brain from hydrocephalus it is often necessary to place a device (shunt) that drains cerebrospinal fluid from around the brain into the abdomen where it can be absorbed. Recent scientific investigations have shown that a procedure performed at the time of surgery for aSAH can decrease the likelihood of developing hydrocephalus requiring a shunt. This procedure involves making a very small connection between one of the fluid spaces in the brain (ventricle) and the fluid surrounding the brain (subarachnoid space). Though the procedure decreases the incidence of shunt-dependent hydrocephalus, its neuropsychological sequelae remain poorly defined. Reducing the incidence of hydrocephalus requiring a shunt is likely to improve patients' quality of life. However, it remains possible that this procedure, which is now widely used, may have unknown adverse effects on emotional or cognitive function. This is a particularly relevant concern given the proximity of the lamina terminalis to important functional regions of the brainstem, forebrain, thalamus, and hypothalamus. We propose to assign patients requiring surgery for aSAH by chance (like a coin-toss) to either:

- 1) receive this procedure (lamina terminalis fenestration) as part of their surgery; or,
- 2) undergo surgery without lamina terminalis fenestration. After surgery, patients will be followed for development of hydrocephalus and to assess their cognitive, neuropsychological, and emotional outcomes over the period of one year. This analysis will allow a more complete comparison of the risks and benefits of lamina terminalis fenestration in patients undergoing surgery for intracranial aneurysms.

a) Hypothesis

Hydrocephalus requiring a permanent diversion of the cerebrospinal fluid (shunt) is a common and significant sequella of aSAH, and contributes significantly to the long-term morbidity of this disease. Microsurgical fenestration of the lamina terminalis during surgery for aneurysm clipping has been shown to reduce the incidence of shunt-dependent hydrocephalus in a previous retrospective study. As a result of this work, the procedure has now commonly employed during aneurysm surgery. The effect of this procedure on long-term patient outcome, however, remains unknown. We believe that, though this procedure may reduce morbidity from hydrocephalus, it may be associated with neuropsychological deficits due to disruption of the delicate circuitry of the basal forebrain, brainstem, and diencephalons. We propose to study this procedure prospectively, in a randomized trial, to examine its effect on the long-term neurological, psychological, emotional, and functional outcomes of patients undergoing surgery for aneurysm clipping. Our primary outcomes will be the long-term morbidity of the procedure and its neuropsychological effects as measured by a variety of assessments and interviews over one year of follow-up. This will include a characterization of the differences between the two groups in level of function, incidence of depression, cognitive assessments, and quality of life. Secondary outcome will be incidence of hydrocephalus requiring shunt placement.

B. Study Population and Recruitment

The composition of the proposed study population as follows: N 70 (35 treatment, 35 no treatment). Age will range from 40 to 70 years. Approximately 67% of the patients will be women, and 32% will be men, based on epidemiological data showing an increased incidence of aSAH in women. Our study population will be representative of the Washington Heights community and surrounding areas, and will be approximately 38% white, 28% Hispanic, 25% black, 5% Asian, 2% Native American, and 2% Pacific Islander. There is an increased incidence of aSAH in women as compared to men, and we expect this to be reflected in study enrollment, though stratification will be used. There is no influence of race on occurrence aSAH, thus we expect the study enrollment to reflect the racial profile of the community served by CUMC.

Inclusion/exclusion criteria will be assessed while obtaining a medical history during admission and through medical chart review.

a) Inclusion

- Patients must be over 40 years of age and less than 70 years of age.
- Patients must be diagnosed with aSAH, Hunt/ Hess grade IV or V, confirmed by CT or LP, with an intracranial aneurysm identified on four-vessel angiography..
- Patients must arrive at CUMC within 48 hours of symptom onset.
- The location of the aneurysm must require a frontosphenotemporal (pterional) craniotomy for aneurysm surgery.

b) Exclusion

- Pre-existing malignancy, rheumatological disease, human immunodeficiency virus (HIV) or organ transplantation. Infection with a definite source.
- Cardiac ischemia.
- Pulmonary embolism.
- Deep venous thrombosis.
- Pregnant women and nursing females.

C. Study Procedures

The surgical procedure will be performed by Dr. Connolly, Associate Professor of Neurosurgery, according to standard protocol. The only modification will be the addition, in the patients randomized to the treatment cohort, of the microsurgical fenestration of the lamina terminalis. This procedure does not add a significant amount of time to the operation and does not carry additional risk beyond that incurred in the aneurysm surgery.

Post-operative management will take place in the Neuroscience Intensive Care Unit (NICU) at CUMC. Patients will be managed according to the standard of care by the NICU staff, including attending neurointensivists, neurosurgeons, and skilled nurses.

Follow-up interviews and neurological exams will be conducted by a neurointensivist and Dr. Michael Schmidt, a neuropsychologist in the Department of Neurology. He will and the research coordinator (ER) will be blinded to the patients' treatment assignments.

A safety monitoring board will be composed of an attending neurosurgeon other than Dr. Connolly, and a non-neurointensivist attending neurologist from the Department of Neurology. Surgical complications and all procedure-related morbidities will be reviewed as they occur. Monthly meeting will also be scheduled to assess progress of the trial.

The alternatives to the procedure in this study are conservative management (i.e., not surgery) or to undergo surgery for aneurysm clipping without entering the study.

D. Blood samples

Approximately 10 milliliters of the subject's whole blood will be collected for analysis daily for 14 days. One tube (5 ml) will be used for serum analyses, and another (5 ml) will be used for plasma analyses. Levels of inflammatory markers and markers of neuronal injury will be assayed from these samples. Whenever possible, blood will be collected from an existing arterial or venous line. If no arterial or venous access is available, peripheral venipuncture will be used to obtain blood samples. All samples will be de-identified by replacing direct patient identifiers with a specific linking code. The key for this code will be stored in a locked room in the research lab.

E. Equipment

Instruments and equipment for the surgical procedure will not differ from the standard of care and will be left to the discretion of the surgeon. For neuropsychological testing and follow-up interviews, a battery of tests, assessments, and interviews will be conducted. This will include the Sickness Impact Profile, Barthel Index, and possibly other tests as clinically indicated. Assessments will occur upon discharge from the hospital following the surgical procedure, and at 3 and 12 months after aSAH. No investigational device or drug will be employed in this trial.

F. Compensation

Subjects will receive no direct compensation for participation in this trial.

G. Risks

Microsurgical fenestration of the lamina tenninalis during aneurysm clipping after SAH has been employed safely in a variety of cases over the past 3 years by Dr. Connolly. There are no known risks directly associated with the treatment. A theoretical risk of disruption of the tissue or neuronal circuitry of the tissue surrounding the third ventricle and lamina terininalis exists. The operative risks in both the treatment and no treatment group are equivalent and consist of the risks associated with the aneurysm surgery. The risks of having blood drawn include soreness and bruising at the puncture site. Sometimes there may be discomfort during the procedure. Occasionally people feel lightheaded or faint. There is a small risk of infection whenever blood is drawn or when a plastic catheter is placed in the vein. The amount of blood to be taken is not considered to be a significant amount, and is therefore not expected to have any significant risk to the patient. Blood draws, if possible, will use an existing arterial or venous line (placed as standard of care) and this will minimize the above risks.

H. Benefits

The use of microsurgical fenestration of the lamina terminalis in conjunction with aneurysm surgery may reduce the risk of developing shunt-dependent hydrocephalus. This, in turn, may improve functional outcome after aSAH-including a possible decrease in incidence of depression, improved cognitive performance, and increased independence in activities of daily living. However, there may be no direct benefit to the patient, as it is not certain that the procedure will help. There is no direct benefit if the patient is in the no treatment group, beyond that associated with the surgery itself. Participation in this study has an indirect benefit of helping healthcare practitioners better understand brain aneurysms and treatment after subarachnoid hemorrhage. This study may lead to better treatments in the future for patients with intracranial aneurysms and bleeding around the brain.

I. Confidentiality

Study records that identify patients will be kept confidential as required by law and the policies governing research at Columbia University. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, the patient will not be identified by name, social security number, address, telephone number or any other direct identifier in study records. Patient records may be reviewed in order to meet federal or state regulations. The investigator, regulatory authorities, and IRB may keep the research records indefinitely. If the results of the study are published or presented at a medical or scientific meeting, the patients will not be identified.