Post-Operative Hydrocephalus in Patients Undergoing Emergent Hemicraniectomy for Elevated Intracranial Pressure (ICP): a retrospective case series of 40 patients

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A. Study Purpose and Rationale

Elevated intracranial pressure (i.e. intracranial hypertension) is a potentially devastating sequela of neurologic injury, often complicating catastrophic brain injury such as deep intracerebral hematoma and hemispheric ischemic stroke. Despite initial compensatory mechanisms, elevated ICP directly leads to mechanical compression and distortion of brain tissue as well as hypoxic-ischemic injury. These changes result in transtentorial or tonsillar herniation with cranial nerve and respiratory dysfunction, coma, and if left unchecked, ultimately death.

Regardless of proximate cause, ICH (intracranial hypertension) is a medical emergency which requires immediate attention. Following early establishment of invasive monitoring of ICP, non-invasive ICP reduction can be achieved medically through a combination of head elevation, hyperventilation, hypertonic therapy, propofol sedation with intubation, mannitol diuresis, and therapeutic hypothermia.

Medical ICP reduction therapy for hemispheric ischemic stroke and deep cerebral hematoma may fail for several reasons. In a minority of cases, failure can be attributed to the fact that most medical therapies lose their efficacy with prolonged use.[i] However, in the majority of cases, failure is simply a consequence of the inability of medical therapy to control the rapid (< 24 hours) increases in ICP seen in hemispheric ischemic stroke and deep intracerebral hematoma. Large hemispheric infarction has a particularly poor response to optimal medical management, with mortality estimated to be between 50 and 78%.[ii,iii] At the point where the medical therapies noted above can no longer maintain ICP in acceptable ranges for a given patient, and surgical correction of the offending insult in not an option (predominantly hemispheric stroke, deep intracerebral hematoma, acute head trauma), attempts to increase the intracranial volume can be implemented. Usually employed as a 'last-ditch' effort to control refractory ICH, hemicraniectomy with durotomy is one such procedure designed to increase intracranial volume. Hemicraniectomy involves removal of the skull over approximately one-half of the head ipsilateral to the lesion, always to the level of the origin of the zygomatic arch/floor of the middle cranial fossa (to afford adequate decompression of the temporal lobe and middle cranial fossa) while avoiding the sigmoid and superior sagittal sinuses (to prevent the possibility of sinus thrombosis).[iv,v] Furthermore, care must be taken to perform a decompression large enough so as not to have the freely swelling brain trap and occlude surface blood vessels (particularly cortical draining veins) against the skull edge.

The rationale of this procedure is to permit brain swelling into a durotomy 'bag', outside the confines of the usual boundary of the skull.[2] Opening the skull vault and allowing the brain to freely 'herniate' outward can allow a reduction in ICP and prevent continuing brain damage by hypoxic-ischemic injury or mechanical distortion of brain tissue. The scalp is then sutured with minimal tension; this removes pressure from the edematous brain on the midline (e.g. brainstem) and contralateral structures. The bone is either kept frozen in antibiotic solution or stored under the patient's own abdominal skin.[vi] To improve cosmetic defects and restore cerebral protection, the bone is replaced at the earliest appropriate time period, which is primarily dependent on the extent of resolution of the patient's intracranial hypertension.

Observational data suggest that rapid and sustained control of ICP via decompressive hemicraniectomy improves outcomes in trauma, hemispheric cerebral infarction, and subarachnoid hemorrhage in carefully selected cases.[vii,viii] Decompressive craniectomy also appears to improve brain tissue oxygenation.[ix] A retrospective analysis evaluating the effects of decompressive hemicraniectomy for traumatic brain injury at one year found that 25% of patients at very high risk of brain death prior to

surgery were able to attain social rehabilitation.[8] Of course, in the absence of randomized, controlled trials, it is difficult to make a definitive judgment of the efficacy of craniectomy in these situations.[x,xi] Numerous reviews have additionally noted that the primary complications of the procedure post-operatively include meningitis, cerebral abscess, and systemic infection.[8]

Since 1998, the principal investigator has been performing hemicraniectomy for elevated ICP following failure of maximal medical management in patients with hemispheric cerebral infarction and deep intracerebral hematoma. Over the course of 40 such cases, the principal investigator has frequently observed the development of hydrocephalus following removal of the bone flap. The observed hydrocephalus is of the communicating subtype, as is evidenced by dilation of both the ventricles and subarachnoid spaces. This hydrocephalus is not thought to be due to the initial neurologic insult, as neither hemispheric cerebral infarction nor deep intracerebral hematoma are associated with hydrocephalus as a sequela. In fact, in the rare scenario where dissection of blood from a hematoma into the ventricular system creates hydrocephalus, this would be due to obstruction of either the cerebral aqueduct or outlet foramina (non-communicating hydrocephalus) and would not produce dilation of the calvarial subarachnoid spaces. Furthermore, patients with these insults successfully treated with strict medical management for elevated ICP do not develop hydrocephalus during or following treatment.

Considering the discussion above, we believe that the observed post-operative hydrocephalus is associated with the decompressive hemicraniectomy procedure. Though this is not the first time post-operative hydrocephalus has been associated with hemicraniectomy, it has only been previously described in theoretical models, animal models, and isolated case reports.[xii,xiii,xiv] These models have suggested that either intraoperative disturbance of the subarachnoid granulations or post-operative obstruction of the lumen of the cortical subarachnoid space by the expanding cerebral mantle may increase the resistance to CSF outflow.[14] Regardless of pathophysiologic etiology, hydrocephalus directly leads to morbidity secondary to elevated ICP as described above. At CUMC, upon diagnosis of hydrocephalus via CT, MRI, or elevated CSF pressure on lumbar puncture, CSF diversion via spinal drain or ventriculostomy is undertaken to normalize ICP.

We hypothesize that communicating hydrocephalus is a potential complication of emergent decompressive hemicraniectomy in the treatment of medically refractory intracranial hypertension secondary to hemispheric cerebral infarction or deep intracerebral hematoma. The establishment of an association between hemicraniectomy and communicating hydrocephalus as well as the identification of potential risk factors which may increase the likelihood of this complication are key additions to the body of knowledge surrounding this procedure. Such data would provide justification for future prospective, controlled studies examining methods of post-operative prophylaxis and treatment of hydrocephalus, the differential efficacy of early versus late intervention, as well as long-term morbidity and mortality associations. While elucidation of the mechanism of hydrocephalus in these patients is an important pathophysiological question, we must stress that this is not a goal of the proposed study.

B. Study Design and Statistical Analysis

In order to fulfill study aims, we propose a retrospective case series which will investigate the development (or lack thereof) of hydrocephalus in 40 patients (ages 20-76, M:F $\approx$ 1:1) who have received hemicraniectomy for hemispheric cerebral infarction (20) or deep intracerebral hematoma (20) at CUMC as performed by the principal investigator since 1998. The principal investigator is the only surgeon at CUMC who performs this procedure and has done so from 1998 to the present. This fact will help to reduce potential observer bias. It is important to note that we will rely upon the literature as a historical control in this study, as hydrocephalus has not been observed in patients receiving medical therapy for elevated ICP.

All patients in the study were admitted to the Neurologic Intensive Care Unit (NICU) at CUMC between 1998 and 2005 with either hemispheric cerebral infarction or deep intracerebral hematoma. For the purposes of the study, hemispheric cerebral infarction includes those patients with middle cerebral artery (MCA) or posterior cerebral artery (PCA) territory infarctions. Deep intracerebral hematoma

includes hematomas which secondary to their location in the brain, were not evacuable by surgical means. Cerebellar hematomas are excluded from this group as they are nearly universally evacuated. The aforementioned diagnoses were made by housestaff and attending physicians in the Departments of Neurology and Neurosurgery based on information obtained from history and physical exam as well as imaging and contrast studies (CT, MRI, MRA, MRV, angiogram). All of the patients in the study developed ICP elevations secondary to their neurologic insult which were initially diagnosed by a combination of CT or MRI scan, signs and symptoms of elevated ICP on physical exam, or invasive ICP monitoring (intraventricular or intraparenchymal catheterization with pressure transduction) showing ICP > 20mmHg. Patients with elevated ICP were treated emergently to reduce ICP via a combination of head elevation to 30˚, hyperventilation to PCO_2 of 24-26mmHg, intravenous mannitol or 3% hypertonic saline, propofol sedation with intubation, and hypothermic therapy to 32-34˚C (in this order, as needed). Invasive monitoring of ICP was maintained during the treatment period in the NICU. In all cases, definitive surgical management designed to treat the proximate cause of ICP elevation was not an option. This determination was made by the attending neurosurgeon.

For all patients in the study, the determination of failure of maximal medical therapy and necessity for hemicraniectomy as a life-saving measure was made by the principal investigator and NICU attending neurologists in the pre-operative period. Following this determination, hemicraniectomy to the level of the zygomatic arch was performed on all patients in the study by the principal investigator in the operating rooms at CUMC. The scalp was sutured with minimal tension and the bone flap was maintained in the abdominal wall. Following surgery, all patients were returned to the NICU for further medical management of their cerebral edema and monitoring of their ICP. During this time, patients received a number of follow-up CT scans and in a subset of cases, had CSF diversionary hardware (e.g. intraventricular catheter, lumbar spinal drain) placed for clinically or radiographically identified hydrocephalus. The majority of patients were eventually discharged with cerebral protection and strict follow-up while a small subset succumbed to their injuries while in the NICU. A small subset of patients returned to CUMC post-NICU discharge with signs and symptoms of elevated ICP, were found to have radiographic evidence of hydrocephalus, and were subsequently treated with CSF diversionary hardware.

For the purposes of this study, communicating hydrocephalus will be defined as radiographic evidence of dilation of the ventricular system and subarachnoid spaces as read by the attending neuroradiologist or evidence of elevated CSF pressure (> 20mmHg) by lumbar puncture. Non-communicating hydrocephalus will be defined as radiographic evidence of dilation of the ventricular system alone as read by the attending neuroradiologist. CSF pressure by lumbar puncture cannot be used to rule-in or rule-out non-communicating hydrocephalus.

In order to determine the association between hydrocephalus and hemicraniectomy, as well as risk factors which may increase the likelihood of hydrocephalus in patients receiving hemicraniectomy, the following statistical analyses will be utilized. To begin, a database will be prepared ascribing 'hydrocephalus' or 'no hydrocephalus' to the 40 cases along with the post-operative day of diagnosis (if applicable). The cases will also be stratified according to the following predictor variables: gender, age, presenting diagnosis, time from presentation to bone flap removal, time from bone flap removal to occurrence of hydrocephalus (if applicable), and side of hemicraniectomy. A univariate T-test will be used to determine associations between hydrocephalus and continuous predictor variables (age, time from presentation to surgery). A Chi-square test will be used to determine associations between hydrocephalus and categorical predictor variables (gender, presenting diagnosis, side of hemicraniectomy). A logistic stepwise regression model can be used to analyze the impact of multiple variables, both categorical and continuous, on the development of hydrocephalus. Finally, Cox proportional hazard ratios can be used to examine the association between predictor variables and the time to development of hydrocephalus in applicable cases. For all statistical analyses, p=0.05, 1-β-0.80.

The investigators are aware that a retrospective analysis of this size has inherent limitations. The number of patients may not allow for statistically significant associations to be made between particular predictor variables (esp. categorical) and hydrocephalus. Secondly, the availability of historical data may at times be limited. Third, there will be inherent variability in the 'maximal medical therapy' received by

each patient prior to surgery, the means by which hydrocephalus was diagnosed in each patient, and the time delay between physiologic development of hydrocephalus and diagnosis. However, should there be preliminary findings that suggest an association between hemicraniectomy and hydrocephalus, a multicenter, prospective analysis which would provide enough patients to allow for more robust statistical analysis would be warranted.

C. Study Procedure

Study subject medical information, including but not limited to diagnoses given, operative reports, daily progress notes, medications administered, and imaging study data will be reviewed on the electronic databases WebCis and Amicas by the investigators. If necessary, medical information will be reviewed in paper form in the Department of Medical Records. CT and MRI scans may also be directly reviewed by investigators in the Department of Radiology. Confidential medical information will be compiled and deidentified in one or more databases (please see **Confidentiality of Study Data** below for information on procedures for safeguarding confidentiality of study data). A *Patient Data Extraction Form* containing the following fields will be utilized to gather study subject medical information: age, gender, presenting diagnosis, time from presentation to surgery, side of hemicraniectomy, operative complications (if any), post-operative complications (if any), +/- development of hydrocephalus, time from surgery to development of hydrocephalus. Database information will then be statistically analyzed as described above.

D. Study Drugs

No drugs will be administered during the course of this study.

E. Medical Devices

No medical devices are under investigation in this study.

F. Study Questionnaires

No questionnaires will be utilized during the course of this study.

G. Study Subjects

Study subjects will include those who received hemicraniectomy as performed by Dr. E. Sander Connelly at Columbia University Medical Center (CUMC) for treatment of medically refractory intracranial hypertension secondary to hemispheric ischemic stroke or deep intracerebral hematoma. Study subjects will initially be identified from Dr. Connelly's records from 1998 to the present.

H. Recruitment of Subjects

No recruitment of subjects will be necessary as the study is retrospective. Study subjects will be identified as described above.

I. Confidentiality of Study Data

Confidential medical information will be reviewed and recorded only if necessary to achieve study aims. All recorded and compiled confidential medical information will be deidentified via removal of subject name, hospital unit number, social security number, telephone number(s), and address(es).

Recorded confidential patient information will be kept in the Principal Investigator's office located at P&S 5-461 in a locked cabinet.

J. Potential Conflict of Interest

There are no potential conflicts of interest. Neither the investigators nor Columbia University have a proprietary interest in the hemicraniectomy procedure or stand to benefit financially from this investigation.

K. Location of the Study

The medical records, operative reports, and imaging studies for all study subjects will be reviewed on the Columbia University Medical Center campus. Offices and reading rooms in the Departments of Radiology, Neurological Surgery, and Medical Records will be utilized.

L. Potential Risks

Given that this is a retrospective case series without therapeutic or other intervention, there are no foreseeable risks to study subjects.

M. Potential Benefits

Study subjects will not receive any direct benefit from their inclusion in the study. However, as described above, an understanding of the clinical relationship between hemicraniectomy and post-operative hydrocephalus as well as the factors which may contribute to post-operative hydrocephalus in this patient population will help provide a basis for future prospective studies.

N. Alternative Therapies

No therapeutic interventions are included under this protocol.

O. Compensation to Subjects

No compensation will be provided to study subjects.

P. Costs to Subjects

No costs will be incurred by study subjects.

Q. Minors as Research Subjects

No potential study subjects were under the age of 18 at the time of surgery.

R. Radiation or Radioactive Substances

Study subjects will not be exposed to radiation or radioactive substances during the course of this study.

S. References

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