Traumatic Brain Injury in Latin America: Lifespan Analysis Randomized Control Trial Protocol*

**BACKGROUND:** Although in the developed world the intracranial pressure (ICP) monitor is considered the standard of care for patients with severe traumatic brain injury (TBI), its usefulness to direct treatment decisions has never been tested rigorously.

**OBJECTIVE:** The primary focus was to conduct a high-quality, randomized, controlled trial to determine whether ICP monitoring used to direct TBI treatment improves patient outcomes. By providing education, equipment, and structure, the project will enhance the research capacity of the collaborating investigators and will foster the collaborations established during earlier studies.

**METHODS:** Study centers were selected that routinely treated ICP based on clinical examination and computed tomography imaging using internal protocols. We randomized patients to either an ICP monitor group or an imaging and clinical examination group. Treatment decisions for the ICP monitor group are guided by ICP monitoring based on established guidelines. Treatment decisions for the imaging and clinical examination group are made using a single protocol derived from those previously being used at those centers.

**EXPECTED OUTCOMES:** There are 2 study hypotheses: (1) patients with severe TBI whose acute care treatment is managed using ICP monitors will have improved outcomes and 2) incorporating ICP monitoring in the care of patients with severe TBI will minimize complications and decrease length of intensive care unit stay.

**DISCUSSION:** This clinical trial tests the effectiveness of a management protocol based on technology considered pivotal to brain trauma treatment in the developed world: the ICP monitor. A randomized, controlled trial of ICP monitoring has never been performed—a critical gap in the evidence base that supports the role of ICP monitoring in TBI care. As such, the results of this randomized, controlled trial will have global implications regardless of the level of development of the trauma system.

**KEY WORDS:** Craniocerebral trauma, Clinical research protocol, Intracranial pressure, Randomized controlled trial

**GENERAL INFORMATION**

**BEST TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure trial)**

Overall study dates: April 2007 to March 2013.

**Funding agency:** NIH/Fogarty International Center/National Institute of Neurological Diseases and Stroke R01 NS058302

**ABBREVIATIONS:** GSC, Glasgow Coma Scale; ICP, intracranial pressure; RCT, randomized, controlled trial; TBI, traumatic brain injury; UW, University of Washington

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RATIONALE AND BACKGROUND INFORMATION

Intracranial pressure (ICP) monitoring per se has never been subjected to a prospective, randomized controlled trial (RCT) to establish its efficacy in improving outcome from severe traumatic brain injury (TBI). Hence, there are insufficient data to support its use as a standard of care. 1

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Current evidence-based recommendations1 are that comatose head injury patients (Glasgow Coma Scale [GCS] score, 3-8) with traumatic mass lesions at admission: older than 40 years of age, unilateral or bilateral motor posturing, or a systolic blood pressure less than 90 mm Hg (Level III). ICP monitoring in patients with a normal CT scan with 2 or more of the following features at admission: older than 40 years of age, unilateral or bilateral motor posturing, or a systolic blood pressure less than 90 mm Hg (Level III). ICP monitoring in patients with a normal CT scan with 2 or more of these risk factors is suggested as an option. Routine ICP monitoring is not indicated in patients with mild or moderate head injury but may be undertaken in certain conscious patients with traumatic mass lesions at the discretion of the treating physician.

Since 2007, the UW, with collaborators from the Oregon Health & Science University; the University of California, San Diego; and Argentina; Bolivia; Colombia; and Brazil, has been conducting an RCT evaluating management of severe TBI using ICP monitoring in the intensive care unit (ICU) at 6 sites in 2 countries (ClinicalTrials.gov identifier: NCT01068522).

In addition, an observational study in 5 countries has focused on the natural course of recovery and outcome. UW Professor Randall Chesnut, MD, is principal investigator for the overall research program. Both the study and this protocol are funded
by a National Institutes of Health National Institute of Neurological Disorders and Stroke/Fogarty-sponsored grant “Traumatic Brain Injury in Latin America: Lifespan Analysis.” The studies are run in collaboration with Fundacion ALAS (Apoyo al lesionado neurologico agudo [Support to the Acute Neurological Patient]), and the Latin American Brain Injury Consortium. As part of the study implementation strategy, we established a local data center in Rosario (Centro de Informatica y Investigaciones Clinica), which performed site training and oversight as well as local data management. Only the RCT protocol is described here.

**STUDY GOALS AND OBJECTIVES**

The primary focus for this scientific investigation is to conduct a high-quality RCT to determine whether ICP monitoring to direct treatment of patients with TBI improves medical practice and patient outcomes.

**Specific Aim**

In a RCT in trauma centers in Bolivia and Ecuador, the aim is to test the effect on outcomes of management of severe TBI guided by information from ICP monitors vs a standard protocol based on imaging and clinical examination.

**Hypothesis 1**

Patients with severe TBI whose acute care treatment is managed using ICP monitors will have significantly lower mortality and better neuropsychological and functional recovery over 6 months post-trauma than those whose treatment is managed with the standard protocol.

**Hypothesis 2**

The incorporation of ICP monitoring in the care of patients with severe TBI will minimize complications and decrease length of stay in the ICU.

**STUDY DESIGN**

**Protocol**

This study is a randomized, outcome-masked, clinical trial of the management of severe TBI, with or without monitoring of ICP. The study is designed to test the effect on outcomes of management in 324 participants at centers in Bolivia and Ecuador and is a 2-group, parallel design. Within 24 hours of injury (or 24 hours of deterioration, but no later than 72 hours after injury), patients with severe TBI are randomized to brain injury management based on ICP monitoring (ICP group) or brain injury management conducted according to a protocol that does not include monitoring of ICP (imaging and clinical examination group). Patients are followed and their outcome evaluated by a blinded examiner at 3 and 6 months after injury.

**METHODOLOGY**

**Study Sites**

The study was initiated at 3 centers in Bolivia. Two were located in Santa Cruz de la Sierra, Bolivia (Hospital San Juan de Dios and Hospital Japones) and 1 in Cochabamba, Bolivia (Hospital Viedma). As the study progressed, we incorporated 3 additional centers: 1 in Tarija, Bolivia (Hospital San Juan de Dios), 1 in Quito, Ecuador (Hospital Eugenio Espejo), and 1 in Guayaquil, Ecuador (Hospital Luis Vernaza).

**STUDY ENROLLMENT PROCEDURES**

**Identifying and Recruiting Candidates for the Trial**

When a TBI patient is received in the participating hospital, he or she is evaluated by an emergency department physician to determine whether he or she fulfills the eligibility criteria listed below. Immediate contact is made with the 24-hour on-call study coordinator, who confirms eligibility and requests consent from the patient’s legally authorized representative.

**Eligibility Criteria**

Inclusion criteria are as follows: admission to study hospital within 24 hours of injury; closed head trauma; GCS score of 8 or less or, if intubated, GCS motor score of 5 or lower on admission, or deterioration to that level within the first 48 hours after injury; no foreign object in the brain parenchyma; randomization within 24 hours of injury (for patients with a GCS score of 8 or less on admission) or within 24 hours of deterioration (patients deteriorating to a GCS score of 8 or less within 48 hours of injury); younger than 12 years of age.

Exclusion criteria are as follows: GCS score of 3 with bilateral fixed and dilated pupils and/or decision to not actively treat before enrollment into study; no beds available in the ICU; no ICP monitor available; pregnancy; prisoner; no consent given; nonsurvivable injury; other (eg, preinjury life expectancy <1 year); and preexisting neurological disability that would confound outcome.

**CONSENT**

Informed consent is obtained by the study coordinator with the site PI. Because the patients are in a coma, consent for those younger than 20 years of age is discussed with the family and for those 13 to 20 years, discussion is with the parent or legal guardian. Written and verbal consent is obtained in Spanish unless the consentee speaks only Aymaran or Quechuan, which have no common written form, then consent is done verbally. Care is taken to include in this discussion not only study issues but also the concept of clinical research, which is quite uncommon in these areas. Whenever the patient regains consciousness, the consent
PROCESS IS REPEATED TO OBTAIN CONSENT (OR CHILD ASSENT FOR THOSE 13-20 YEARS) TO CONTINUE.

RANDOMIZATION

The randomization lists, computer generated by the statistician/database manager at the UW Data Center, are blocked for balance and stratified by site, age (40 years or younger vs older than 40 years), and the GCS score (3-5 vs 6-8, or GCS motor score 1-2 vs GCS motor score 3-5 if intubated). Randomization is routinely implemented using a password-protected application on a laptop at each site. If the computer is not available when it is time to randomize a patient, the study coordinator calls a study monitor at Fundacion ALAS who flips a coin and tells the site the group assignment. The Monitor sends an e-mail indicating the assignment to the UW Data Center as well as the site to confirm the assignment.

STUDY INTERVENTIONS

Interventions, Administration, and Duration

TREATMENT ARMS

There are 2 arms in this study, the ICP monitor group and the imaging and clinical examination group. Management of patients who are randomized to the ICP monitor group was based specifically on the presence of intracranial hypertension and followed the Guidelines for the Management of Severe Brain Injury.1

Because there is no literature base from which to derive a management protocol for severe TBI patients being treated without ICP monitoring, we developed an ad hoc protocol in conjunction with the investigators at the 3 initial sites. Fortunately, they had developed similar treatment approaches at their institutions, and it was possible to formulate a protocol acceptable to all. One criterion for subsequent acceptance of institutions as study centers was acceptance of this protocol by all involved in the care of severe TBI patients. (In the absence of a supporting literature base or common consensus in this area, this acceptance criterion was not trivial and resulted in exclusion of 1 group).

OVERALL TREATMENT GUIDELINES (BOTH GROUPS)

During this study, we strongly encouraged the following treatment approaches whenever available and/or possible:

a. Patient monitoring measures
   i. Place patient on mechanical ventilation
   ii. Place continuous SaO₂ monitor and ETCO₂ monitors
   iii. Insert indwelling urinary catheter to monitor urine output
   iv. Insert arterial catheter for arterial mean pressure monitoring
   v. Insert central venous catheter for infusion of solutions and central venous pressure monitoring
   vi. Monitor neurological clinical status each hour: pupils, GCS score, vital signs, etc.
   vii. Brain CT (see below)

b. General measures
   i. Head positioning at 30 degrees
   ii. Head and neck in neutral position and aligned
   iii. Avoid hyperthermia
      1. Defined as central temperature 38°C or higher
         a. Nondrug measures (cooling)
         b. Dipirona (metamizole sodium)
   iv. Early enteral nutritional support
      1. Before 48 hours
      2. 25 kcal/kg weight
   v. Pharmacological prophylaxis of posttraumatic seizures
      1. Phenytoin (intravenously or orally)
         a. Load and maintenance dose as is being given in each hospital
      vi. Gastric bleeding prophylaxis
         1. Ranitidine or omeprazole
      vii. Avoid decubitus lesions
      viii. Deep venous thrombosis prophylaxis
      ix. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections
      x. Maintain hemoglobin 7 mg/dL or higher

c. Routine CT scans
   i. First CT: on hospital admission
   ii. Second CT: 48 hours after the first CT
   iii. Third CT: 5 to 7 days after the first CT

Imaging and Clinical Examination Group

Treatment decisions for the imaging and clinical examination group are made following the protocol developed for this study (Figures 1 and 2). A detailed description of the protocol manual of procedures is found at the study Web site (www.globalneurotrauma.org).

ICP Monitor Group

Treatment decisions for the ICP monitor group are made following protocols based on the Guidelines for the Management of Severe Traumatic Brain Injury.1 A tiered approach to interventions was followed, with lower risk therapies used before riskier ones. A detailed description of the protocol Manual of Procedures is found at the study Web site (www.globalneurotrauma.org).

OUTCOMES

Primary Outcome

The primary outcome is a composite measure based on individual outcome variables indicated below. For each measure, the participants are ranked from 1 (worst) to n (best). Those who died are given the lowest ranking, and, for the neuropsychological measures, those who are so neurologically impaired that they cannot perform the test are given the next lowest rankings. Tied ranks are all given the average of the tied ranks. For example if there are 3 deaths, all are given the rank 2.
(the average of 1, 2, and 3). To increase interpretability, the ranks are converted to percentiles, giving the percentage at or worse than the participant’s score. For each person, the percentiles on the different measures are averaged.²

**Outcome Variables (Table)**

- Mortality
- Time to follow commands (measured as time from injury to following simple commands as defined by a score of 6 on the GCS motor scale)
- The Galveston Orientation and Amnesia Test Sum of Errors³ at discharge and 3 and 6 months after injury
- Functional status at 3 and 6 months (see below for further definition)
- Neuropsychological Test Battery (see below for individual measures).

**Functional Status**

A portion of the Disability Rating Scale⁴ measuring eye opening, communication ability, and motor response, and the Glasgow Outcome Scale Extended⁵ are used to measure the level
of functioning in everyday life. These are the 2 most commonly used measures of functional outcome in TBI. Both have been translated and used extensively in previous research in Latin America by this research group.

**NEUROPSYCHOLOGICAL TEST BATTERY**

A battery of measures that examine important neuropsychological constructs sensitive to the integrity of brain functions, including TBI, was used. Cognitive, performance-based measures were included because they are sensitive to the effects of TBI and often the major cause of disabilities.

At discharge and at 3 and 6 months, the Galveston Orientation and Amnesia Test (a measure of orientation and amnesia) was administered.

The neuropsychological domains and the measures used at 6 months to examine them are as follows: mental state (Mini-Mental State Examination), working memory (Paced Auditory Serial Addition Test [first subtest only]), speed of information processing (Wechsler Adult Intelligence Scale III Digit Symbol, and Symbol

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**FIGURE 2.** Schematic for the neuroworsening protocol for the imaging and clinical examination group. CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; TBI, traumatic brain injury.
Search subtests\textsuperscript{10,11}, Color Trails Part 1\textsuperscript{12}, Trail Making Test Part A\textsuperscript{13}, episodic memory and learning (Spanish Verbal Learning Test,\textsuperscript{14} Brief Visuospatial Memory Test Revised\textsuperscript{13,15,16}), executive functions (Noun Fluency [animals],\textsuperscript{17} Verbal Fluency [actions],\textsuperscript{18} Controlled Oral Word Association Test,\textsuperscript{19} Color Trails Part 2\textsuperscript{12,13}), and motor speed and dexterity (Grooved Pegboard Test).\textsuperscript{3}

**Primary Outcome Composite**

Scores used in the composite measure include time to follow commands at discharge, Galveston Orientation Amnesia Test, Glasgow Outcome Scale-Extended, and Disability Rating Scale at 3 and 6 months, and the neuropsychological battery at 6 months (Table). The neuropsychological battery includes the Mini-Mental State Examination total score, the Spanish Verbal Learning Test total learning score, Long Delay Free Recall, the Brief Visuospatial Memory Test Revised total learning number correct and delay correct, WAIS III Digit Symbol and Symbol Search scores, Color Trails 2 time to completion, number correct on Paced Auditory Serial Addition Test and 3 subcomposite scores in which tests are grouped together to each form 1 variable to be entered into the composite. The first is composed of the Grooved Pegboard dominant and nondominant times. The second subcomposite is composed of Color Trails Part 1 and Trail Making Test Part A times to completion. The third subcomposite is composed of total correct on Controlled Oral Word Association Test, Category Fluency Test for Animals, and Actions. Before ranking and entering the composite (or subcomposite), each neuropsychological test score will be regressed on age, sex, and years of education, factors known to affect neuropsychological performance, to decrease variability. The residuals are ranked and entered in the composite or subcomposite. Use of T scores based on the norms for monolingual Spanish speakers was considered but discarded because uninjured Bolivians did not have scores with the expected mean of 50, and there was a substantial relationship between years of education and the T scores for some measures.

**DISCUSSION**

Globalization encourages international scientific collaborations, and the successful implementation of this RCT underscores both the capacity and willingness of low- and middle income countries investigators to conduct rigorous Class I trials. Challenges included occasional language/translation barriers, import/export delays, communication challenges, transaction fees associated with multiple currencies, and additional levels of review associated with multinational research. An overview of operational issues relevant to conducting RCTs in low- and middle-income countries will be published separately.

**Trial Status**

Follow-up visits and data collection were ongoing at the time this article was written.

**SAFETY CONSIDERATIONS**

**Data and Safety Monitoring Plan**

The PIs at each site are notified immediately by the study coordinators of any serious adverse event and evaluate whether adverse events are unusual given the patient’s injury. All serious adverse events are reported to the local institutional review boards and to the Data Coordinating Center.

**Serious Adverse Event Reporting**

All serious adverse event data are recorded and analyzed to identify safety problems that may not be readily apparent on a case-to-case review of medical information.

**Data Safety and Monitoring Board**

The study operates under a data safety and monitoring board that provides overall study oversight and an additional level of patient safety review.

**Follow-up**

Subjects were followed for outcome assessments at 3 and 6 months after injury as well as data collection out to 6 months for serious adverse events. Outcome examiners were masked to the treatment group. The study provided no additional treatment after the person left the hospital.

**DATA MANAGEMENT AND STATISTICAL ANALYSIS**

**Data Analysis**

For hypothesis 1, testing will be by a blocked Wilcoxon test\textsuperscript{18} comparing the average percentiles for the subjects in the 2
treatment groups after controlling for center, TBI severity group, and age group. A 2-sided .05 significance level will be used. Analysis will be according to the intention-to-treat principle, i.e., all randomized cases will be followed and included with their assigned treatment group regardless of the management protocol actually used. To supplement the composite test of the overall hypothesis, individual measures will be summarized for each group.

One interim analysis was planned after half of the patients reached the 6-month assessment to determine efficacy. The interim analysis used O’Brien-Fleming boundaries to decide whether to terminate because of a positive effect of ICP-guided management. In addition, to terminate early because of efficacy, analysis of at least 1 of the individual outcomes—mortality or Glasgow Outcome Scale—must have indicated significant improvement with ICP-guided management at the 1-sided nominal .05 level. Because this is a trial for which, in the United States at least, there is strong feeling that the experimental treatment (ICP monitoring) is superior, the study would not be stopped early for futility because it is unlikely to show a significantly positive effect of ICP monitoring. If that is the case, the study needs as narrow a confidence limit as possible, so stopping early would be contraindicated. These criteria were not met at the interim analysis, and the study has been allowed to continue.

For hypothesis 2, length of stay in the ICU will be analyzed using a blocked Wilcoxon test as above. The most frequent complications (major respiratory problems, sepsis, decubitus ulcers) as well as any non-neurological complication will be summarized as present/absent and analyzed separately using a Mantel-Haenszel test with stratification as above. A 2-sided significance level of .01 will be used for each test to account for the multiple comparisons.

POWER

A sample size of 324 patients (162/group) gives the study 80% power to detect an average improvement of 10 percentage points on the percentage with good or moderate recovery on the Glasgow Outcome Scale accompanied by similar improvement on the other outcome measures.

QUALITY ASSURANCE

This team has substantial experience in all elements necessary to successfully conduct high-quality RCTs: representative samples, adequate random assignment, outcome assessment blinding, high follow-up rate, and attention to potential errors. Latin American key investigators new to the team were formally trained in clinical research, including, for some, Master degree and year-long certificate programs and clinical research rotations. Data quality was managed by accuracy checks of every data point and tallying errors until an acceptable level was reached and then maintained through systematic audits. In addition to weekly conference calls among members of the research and administrative team, we hold annual all-team meetings to reinforce training, troubleshoot problems, and encourage collective ownership and responsibility.

Monthly phone calls are held with outcome examiners to provide continued feedback to encourage high follow-up rates and completeness and accuracy of results. These efforts have produced good results including data error rates less than 1% and a current follow-up rate of 92%. In addition to 4 study-appointed clinical and data quality monitors, external review occurs through regular meetings of the data safety monitoring board to monitor the study overall.

Expected Outcomes of the Study

This clinical trial tests the effectiveness of management based on technology considered pivotal to brain trauma treatment in the developed world: the ICP monitor. An RCT of ICP monitoring has never been performed. As noted in every edition of the Guidelines for the Management of Severe Brain Injury, this is a critical gap in the evidence base that supports the role of ICP monitoring in TBI care. As such, the results of this RCT will have global implications regardless of the level of development of the trauma system. It is anticipated that the results will be published during the final quarter of 2012. They are to be presented during the annual meetings of the Congress of Neurological Surgeons and the Neurocritical Care Society in October 2012.

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Ethics
For more than 2 decades, calls for an RCT on ICP monitoring were countered by ethical concerns about an unmonitored control group. Having personally expressed such concerns, the authors were apprised of the high-income countries-centered nature of this objection when, in the process of developing a separate prospective severe TBI outcome study, they encountered Latin American intensivists and neurosurgeons who rarely used such monitoring and were at equipoise about its utility. Ventricular catheter-based monitoring was universally available, so resource limitations did not play an absolute role in this choice. They did not believe that this practice would alter significantly over the next 5 years and expressed interest in establishing the efficacy of ICP monitoring in their setting. Reflecting this equipoise, we designed this RCT. It was subsequently reviewed and accepted by the National Institutes of Health, the UW Institutional Review Board, and the Federalwide Assurance-approved ethics committees/institutional review boards at all study centers.

Disclosures
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COMMENTARY
Commentary provided by Nino Stocchetti available online.