Intracranial Pressure Monitoring in Severe Traumatic Brain Injury in Latin America: Process and Methods for a Multi-Center Randomized Controlled Trial

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Abstract

In patients with severe traumatic brain injury (TBI), the influence on important outcomes of the use of information from intracranial pressure (ICP) monitoring to direct treatment has never been tested in a randomized controlled trial (RCT). We are conducting an RCT in six trauma centers in Latin America to test this question. We hypothesize that patients randomized to ICP monitoring will have lower mortality and better outcomes at 6-months post-trauma than patients treated without ICP monitoring. We selected three centers in Bolivia to participate in the trial, based on (1) the absence of ICP monitoring, (2) adequate patient accession and data collection during the pilot phase, (3) preliminary institutional review board approval, and (4) the presence of equipoise about the value of ICP monitoring. We conducted extensive training of site personnel, and initiated the trial on September 1, 2008. Subsequently, we included three additional centers. A total of 176 patients were entered into the trial as of August 31, 2010. Current enrollment is 81% of that expected. The trial is expected to reach its enrollment goal of 324 patients by September of 2011. We are conducting a high-quality RCT to answer a question that is important globally. In addition, we are establishing the capacity to conduct strong research in Latin America, where TBI is a serious epidemic. Finally, we are demonstrating the feasibility and utility of international collaborations that share resources and unique patient populations to conduct strong research about global public health concerns.

Key words: international; intracranial pressure monitoring; randomized controlled trial; traumatic brain injury

Introduction

FOR OVER 30 YEARS the academic community in high-income countries (HICs) has believed that monitoring intracranial pressure (ICP) is necessary to direct aggressive management of severe traumatic brain injury (TBI). However, with respect to improving patient outcomes, the efficacy of basing treatment on monitored ICP values has never been tested in a randomized controlled trial (RCT). In the third edition of the guidelines for the management of severe traumatic brain injury (Bratton et al., 2007), the evidence base for the recommendation to monitor ICP in the severe TBI patient with an abnormal computed tomography (CT) scan, although indirect, was derived from only two studies: a moderate-

quality RCT (Eisenberg et al., 1988), and a good-quality cohort study (Palmer et al., 2001). The guidelines concluded that the key topic for future investigation was an RCT of ICP monitoring, but also stated, "it is unlikely considering that most TBI experts consider ICP or CPP [cerebral perfusion pressure] parameters to be the primary basis for ICU management decisions in the care of the severe TBI patient" (Bratton et al., 2007).

Globally, most clinicians who manage neurotrauma assess intracranial pressure without ICP monitors, and use ICP management protocols triggered by clinical or CT indicators, rather than monitored pressures. This condition exists in many trauma centers in Latin America. In centers that do not practice ICP monitoring, there is frequently equipoise with

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respect to the utility of adding such technology. Clinicians are unclear whether the general use of ICP monitoring in management would benefit the TBI population in general, and more specifically, which patients would benefit most. In keeping with the growing number of publications from within industrialized nations that ask similar questions about ICP monitoring (Cremer et al., 2005; Shafi et al., 2008; Stuart et al., 1983), this position of equipoise appears to be consistent with the global status of the literature on this topic. Thus these are important questions in resource-rich environments as well as in low- to middle-income countries (LMICs).

This project was conceived in response to the National Institutes of Health (NIH) Fogarty International Center (FIC) program "Brain Disorders in the Developing World: Research Across the Lifespan." The purpose of this project is to test the influence on outcomes, measured at intensive care unit (ICU) and hospital discharge, and at 3 and 6 months post-trauma, of the use of the ICP monitor to direct management of patients with severe TBI. This is an RCT being conducted in six centers: four in Bolivia and two in Ecuador. We hypothesize that patients with severe TBI whose acute care treatment is managed using ICP monitors will have significantly lower mortality and better neuropsychological and functional recovery at 6 months post-trauma than those whose treatment is managed with the standard protocol. Further, we predict that incorporation of the ICP monitor into the care of these patients will minimize secondary complications and decrease length of stay in the ICU.

In addition, a mandate of the FIC's brain disorders program is to build capacity in LMICs to conduct high-quality research about brain pathologies that constitute important public health problems in their communities. The goal of the program is to collaboratively establish independent, self-sustaining, and productive research centers. The following describes the process in which we are engaged to accomplish that goal, and to test our hypotheses.

Methods

Study overview

Background. The Neurotrauma Research Group (NTRG) is a collaboration of clinicians and scientists from Hospital de Emergencias "Dr. Clemente Alvarez" (Rosario, Argentina), Hospital Nacional Professor Alejandro Posadas (Buenos Aires, Argentina), University of Washington (Seattle, WA), and Oregon Health & Science University (Portland, OR). Since 2000 the NTRG has been conducting research about TBI in Latin America (Argentina, Bolivia, Brazil, Colombia, and Ecuador).

After meetings with the Latin American Brain Injury Consortium (LABIC) in La Paz, Bolivia (February 2004) and Curitiba, Brazil (October 2004), the group committed to conduct a study that would randomize severe TBI patients either to ICP monitor placement and subsequent treatment based on monitored values, or to the standard care that directs ICP treatment without monitoring.

Pilot phase and center selection. The NTRG had applied for and had been awarded funding to conduct a pilot study about TBI in Latin America, through an R21 mechanism offered by the FIC's brain disorders program. The goal of the pilot was to assess treatment guideline implementation, and

the influence of guidelines on outcome from TBI in pediatric patients. The R21 was a precursor to submitting an application for a fully developed R01 proposal. As ICP monitoring is necessary in order to follow the guidelines, the NTRG decided to propose the ICP monitor trial as their R01 submission. After a second pilot feasibility study, funded by Fundación ALAS (Wings Foundation, Rosario, Argentina), three centers in Bolivia were selected for the trial: two in Santa Cruz de la Sierra and one in Cochabamba. The selected centers did not use ICP monitors. During the pilot they recruited the expected number of patients, and demonstrated their ability to successfully collect data and follow research protocols.

After 16 months of patient accession, one additional center in Tarija, Bolivia was incorporated. Subsequently, two centers in Ecuador, one in Quito and one in Guayaquil, received approval to be a part of the trial.

Funding. A grant application to carry out the trial was written and submitted in May 2006 under the FIC's program "Brain Disorders in the Developing World: Research Across the Lifespan." Funding began in April 2007, with the National Institute of Neurological Disorders and Stroke (NINDS) providing the majority of the support. In addition, Integra Life Sciences Corporation contributed unrestricted funds and the monitors and disposable supplies required to conduct the trial.

Structure, responsibilities, and oversight. Randall Chesnut is the overall principal investigator (PI), and Carlos Rondina is the Latin America PI. A data and safety monitoring board (DSMB), appointed by and reporting to the NINDS, oversees the conduct of the study and the safety of the patients. A coordinating center at Fundación ALAS is responsible for translating the manual of procedures (MOP) and case report forms (CRFs) into Spanish, training site investigators, monitoring the activities of the sites and the quality of the data they are collecting, and entering the data into the study database. The data center at the University of Washington (UW) is responsible for writing the English version of the MOP and CRFs, generating the randomization programs, developing and managing the database, providing reports for the DSMB, and planning and carrying out data analyses.

Setting. Two of the study sites, Hospital Japones and Hospital San Juan de Dios, are located in Santa Cruz de la Sierra, Bolivia. Hospital Japones has a 6-bed ICU and 180 beds in the general ward. Hospital San Juan de Dios has a 7-bed ICU and 270 beds in the general ward. Together they serve a population of about 1,600,000 people. The third study site is Hospital Viedma in Cochabamba, Bolivia. It has a 9-bed ICU and 320 beds in the general ward, and serves about 1,110,000 people. The fourth study site is also called Hospital San Juan de Dios, and is in Tarija, Bolivia. It has a 6-bed ICU, 250 beds in the general ward, and serves about 600,000 people. The fifth site is Hospital Eugenio Espejo in Quito, Ecuador. It has 12-bed ICU, 446 beds in the general ward, and serves about 1,500,000 people. The sixth site is Hospital Luis Vernaza in Guayaquil, Ecuador. It has a 37-bed ICU, 836 beds in the general ward, and serves about 2,000,000 people.

In Bolivia, approximately 65% of the population lives at or below poverty level, and there is a 25% illiteracy rate. Twenty percent of the population is indigenous, 55% is of mixed race,

15% is Caucasian, and 10% is other. In Ecuador, about 45% of the population lives at or below poverty level, and there is a 10% illiteracy rate. Twenty-five percent of the population is indigenous, 55% is of mixed race, 10% is Caucasian, and 10% is other.

Study site team structure. The study team for each site includes a PI and co-PI, a study coordinator who is also the acute care data collector, and two data collectors for outcome assessments.

Study design. This is an RCT with blinded evaluation of outcome. It has a two-group parallel design. By the nature of the study, the interventions were not blinded.

Subjects

Inclusion/exclusion criteria. Patients admitted to the emergency department (ED) are screened for eligibility (Table 1). The screening includes basic information about the person's injury before and after admission to the study hospital. For eligible patients who do not consent, the screening provides information about the severe TBI population against which we can compare our consented study group, for the purposes of understanding external validity.

Randomization. A patient is received in the participating hospital, evaluated by an ED physician, and identified as possibly meeting study criteria. Immediate contact is made with the 24-h on-call study coordinator, who confirms study eligibility and requests consent from the patient's legally authorized representative. After obtaining consent, the coordinator logs on to a secure database, verifies his or her identity, and provides information about the subject to confirm eligibility and to determine the stratum. In addition to center, randomization is stratified by age (<40 years versus ≥ 40

years), and Glasgow Coma Scale score (GCS) (3–5 versus 6–8). Randomization is blocked within each stratum to ensure balance. The program enters the subject information on the randomization log, retrieves the next assignment for that center and stratum, enters that on the randomization log, and sends the assignment to the study coordinator.

Treatment: Intervention and standard care

Intervention group. Dr. Chesnut trained the neurological surgeons involved with the trial in the technique of inserting the catheter of the ICP monitor. We instructed the ICU groups at each institution, including investigators, associated intensive care physicians, and ICU nursing staff, in the care and interpretation of the implanted device. We provided formal and informal instruction in the physiology of ICP, and the concepts involved in the management of intracranial hypertension (ICH) and altered CPP. This training was conducted during the start-up phase, and is reinforced during return visits for the duration of the study. The management algorithm provided for the intervention group was based on the "Guidelines for the Management of Severe Traumatic Brain Injury" (Bratton et al., 2007). The definition of treatable ICH was an ICP > 20 mm Hg for > 5 min. The definition of failure of a treatment maneuver was the lack of an appropriate lowering of the ICP to ≤ 20 mm Hg within 20 min. The ICP monitor could be removed if the ICP remained ≤ 20 mm Hg for 24 h without ongoing interventions directed at altering it.

Since this was an RCT using an invasive monitor in the experimental group, we wanted to minimize the risk associated with implantation of the device. The literature supports a much lower hemorrhage rate with intraparenchymal than ventricular devices, and there has never been a documented infection with the former. In addition, the guarantee of consistent, continuous involvement of the neurosurgeons required to implant such devices supported our choice of the device with minimal implantation procedural and maintenance demands. Finally, the intraparenchymal device was granted us at no cost, and its accuracy is independent of variables such as clogging or improper leveling of the transducer, which complicate the use of ventricular devices.

Standard care group. We determined the treatment algorithms currently employed in the care of severe TBI patients by interviewing the participating intensive care physicians at each study center. In November 2007, we met with the investigator teams from all centers as a group to codify a treatment algorithm for managing non-monitored patients that would be acceptable and capable of being performed in all settings. Since there has never been an evidence report done on managing severe TBI in the absence of ICP monitoring, and since very little literature exists on this topic, we had little guidance in developing this algorithm. Because these physicians routinely care for such patients, their particular experience and individually-defined management schemata presented the most rigorous background material available. In the absence of comparative studies, resolving differences in management approach among the participating physicians, and systematizing such issues as medication amounts and scheduling became a *de facto* consensus project of considerable proportion. Since this is a treatment protocol without quantitative feedback, issues that required

TABLE 1. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- Traumatic brain injury
- GCS score ≤ 8 (or GCS motor score ≤ 5 if verbal or eyes cannot be assessed) on admission or within first 48 h after injury
- Admission to study hospital within 24 h of injury
- No foreign object in the brain parenchyma
- Age > 12 years
- Randomized:
 - within 24 h of injury [for patients with GCS score < 8 on admission] or within 24 h of deterioration [patients deteriorating to GCS score < 8 within 48 h of injury]

Exclusion criteria

- GCS score of 3 with bilateral fixed and dilated pupils
- No consent
- Pregnant
- Prisoner
- No beds available in ICU
- No intra cranial pressure monitor available
- Non-survivable injury
- Other (e.g., Pre-injury life expectancy under 1 year)
- Pre-existing neurological disability that would not allow selection/follow-up

GCS, Glasgow Coma Scale Score; ICU, intensive care unit.

standardization included the indications for treating ICP based on the clinical examination and the CT scan; duration of empirical treatment; necessity, timing, and interpretation of follow-up CT imaging; and definition of neurologic worsening that would prompt escalation of therapy. Through a judicious and concerted effort, an algorithm was created of which about 20% required later refinements or amendments to become the final management algorithm for the standard care group. This algorithm became the shared approach for managing the standard care group at all study centers.

Baseline and acute data collection

After the patient is enrolled in the study, information is collected about demographic characteristics, pre-injury educational level, living situation, main activity, income, alcohol and drug use, and medical history, typically from family members. The Abbreviated Injury Score (AIS) is recorded based on the first 24 h post-injury. Physiological variables recorded at or soon after admission include initial GCS score, hypotension, hypoxia, pupillary reactivity, and CT scan findings.

Vital signs and Therapeutic Intensity Level (TIL) are collected on an hourly basis for each day the patient is in the ICU, for the full duration of treatment. Additional information such as deterioration in condition, neurosurgery and other surgery, serial CT scan results, and complications are collected until hospital discharge. At discharge, information is collected including the date, neurological status, and discharge destination.

Serious adverse events, adverse events possibly related to study intervention and their resolution, as well as dates of consent by participant, withdrawal of consent, last study contact (for those who were not followed at 6 months post-injury), date and cause of death, and protocol violations are collected at any time during the course of an individual's participation in the study. All serious adverse events are reported within 24 h of occurrence.

Outcome measures

The outcome of the study will be tested by a composite score based on measures of functional status and a battery of neuropsychological tests. A brief description of the measures follows.

Functional status measures. The Disability Rating Scale (DRS) and the Glasgow Outcome Scale-Extended (GOS-E) are used to measure functioning level in everyday life. The DRS (Rappaport et al., 1982) is a brief measure of impairment, disability, and participation. The GOS-E (Wilson et al., 1998) is the most commonly used measure of functional outcome in TBI. Both measures have been translated and used extensively in previous research in Latin America.

Neuropsychological test battery. A battery of measures that assesses important neuropsychological constructs that are sensitive to the integrity of brain function in TBI patients is used, based on the literature and the UW investigators' prior work with TBI patients. In choosing the specific measures, the considerations were that: (1) they cover different aspects of functioning that are clinically relevant and likely to be affected by head injury; (2) the measures possess good psychometric

properties with respect to sensitivity, validity, and reliability; (3) the measures are appropriate for use with a broad spectrum of head injury severity, and are likely to be responsive to treatment effects directed at improving outcomes, and; (4) most importantly, the measures have been translated, adapted, and validated for use with Spanish speakers (Artiola-i-Fortuny et al., 1999, Cherner et al., 2007).

The following measures examining different cognitive constructs are included in the battery. Mental status is examined by the Mini Mental State Examination (Strauss et al., 2006). Working memory is assessed by the first subtest of the Paced Serial Addition Test (Heaton et al., 2004), and Spatial Span of the Wechsler Memory Scale III (Wechsler, 1997). Speed of information processing is assessed by the Wechsler Adult Intelligence Scale III Digit Symbol and Symbol Search subtests (Wechsler, 1997), the Trail-Making Test A (Reitan and Wolfson, 1993), and Color Trails Part 1 (Maj et al., 1993). Memory and learning are assessed by the Spanish Verbal Learning Test (Artiola-i-Fortuny et al., 1999), and the Brief Visuospatial Memory Test Revised (Benedict, 1997; Cherner et al., 2007). Executive functions are tested by Color Trails Part 2 (Maj et al., 1993), the verbal fluency tasks Animals (Gladsjo et al., 1999), Actions (Woods et al., 2005), and the Controlled Oral Word Association Test with the letters P, M, and R (Artiola-i-Fortuny et al., 1999). Motor speed and dexterity of the upper extremity is measured with the grooved pegboard (Klove, 1963). All test instructions and relevant stimuli were adapted using translation and back-translation by bilingual professionals, and the resulting versions were reviewed by native speakers from several Spanish-speaking countries to ensure that the language is neutral and understandable.

Personnel training and set-up

Prior to initiating this trial, the NTRG had conducted a 3-year, multi-center observational study, during which time a cadre of research personnel was trained in the basic concepts of conducting good research. Further, with a research training grant from the FIC (D43 TW007566), we formally trained a core group, including two with Master in Clinical Research degrees received in the United States, as well as year-long research training certificate programs at universities in Argentina and Bolivia, and individual fellowship rotations for some of the personnel from each study site at our main research lab in Rosario, Argentina. Thus, key members of the research team are highly trained and experienced.

A comprehensive training program specific to this study was conducted, including introductory meetings as well as multiple training sessions that targeted each phase of the patient-related interactions during the study: screening in the ED, consenting family members, randomization, placement of the ICP catheter, acute care data collection, provision of treatment and standard care protocols, in-hospital assessments, and post-discharge follow-up for outcome assessments.

Outcome assessments include measures of functional status administered at 3 and 6 months post-injury and a neuropsychological test battery administered at 6 months. Two Latin American physicians (Drs. Petroni and Lujan) with prior training and extensive study experience in outcome measurements trained and certified the outcome examiners in the administration of the functional status measures. Staff from

the Department of Psychiatry at the University of California at San Diego (UCSD) provided Drs. Petroni and Lujan a week-long training session on the standard administration and scoring of the neuropsychological test battery. They were certified at the end of that process, and they then trained the outcome examiners to administer the neuropsychological assessments. Upon demonstrating proficiency, these examiners were subsequently certified by UCSD staff.

Each site was surveyed for resource availability. Computers and peripherals were purchased or upgraded, and internet connectivity secured. A pharmacy service was created to ensure that all study patients had access to the necessary medicines.

Data quality and monitoring

The data collectors use paper CRFs to record the data. One copy is kept at the study site and one is sent to the data entry center in Rosario, Argentina. The data are entered into an Access database with range checks on each variable. The data are entered twice by two different people, with electronic data checks for discrepancies, and the second enterer confirming which value is on the form.

Initially, quality of acute care data was monitored by two members of the study team (Drs. Petroni and Lujan) who visited each site monthly, and audited by pulling hospital records and comparing each data point to those recorded on the CRFs. Errors were used as opportunities to further train the data collectors. In December of 2009 an error tally demonstrated an error rate of less than 1%, after which the monitoring visits were reduced to once every 3 months.

The quality of the outcome data is monitored in the following manner. All data collected are scanned and sent to Rosario, UW, and UCSD to check accuracy. Functional status measures are double-checked and corrected at Rosario. The administration, scoring, and coding of neuropsychological measures are double checked and corrected by investigators at UCSD and UW. A bilingual psychometrist at UCSD provides written feedback to the outcome examiners to point out any errors in test administration or scoring, or to reconcile other discrepancies, in order to provide further training to the examiners. Conference calls take place once a month with each site to review the feedback for recent cases and discuss any concerns. The corrections of neuropsychological measures are then sent to Rosario, where the paper forms are corrected and the data entered. Inter-rater reliability tests were conducted during site monitoring visits, which occurred at least every 3 months.

Ethical committee approval

The study was approved by the local ethical and institutional review board (IRB) committees and the UW IRB. All IRBs not initially possessing Federal Wide Assurance (FWA) approval from the U.S. Office of Health and Human Services (e.g., the IRBs in Bolivia and Ecuador) applied for and received such approval prior to approving the study.

Data analysis

Data analysis for the primary hypothesis will be carried out based on the intent-to-treat principle. All randomized cases will be included in their assigned group regardless of the

treatment approach actually used. To test the hypothesis, we will form a composite of the outcomes of interest, including mortality, time to follow commands, length of post-traumatic amnesia, measures of functional level obtained at 3 and 6 months after injury, and neuropsychological performance obtained at 6 months after injury. To form the composite, scores on each measure are ranked separately from 1 (worst) to n (best). The ranks are converted to percent scoring worse than the participant on that measure to allow for missing scores and to aid interpretability. For each participant, these percentiles are averaged across all the measures (O'Brien, 1984). Death is considered to be the worst outcome on measures for which death precludes assessment, and being too neurologically impaired to be tested is considered to be next worst on the neuropsychological measures. We compare the average percentiles of the assigned treatment groups using a blocked Wilcoxon test controlling for center, TBI severity group, and age group. A two-sided significance level of 0.05 will be used. The analysis of the composite will be supplemented by summarization of the individual measures for each group. One interim efficacy analysis is planned 6 months after half of the full sample size has been entered.

The secondary hypothesis that incorporation of ICP monitoring will minimize complications and decrease length of stay in the ICU will be tested using blocked Wilcoxon tests for continuous outcomes, or Mantel-Haenszel tests for binary outcomes. Factors controlled will be the same as for the primary hypothesis. A two-sided significance level of 0.01 will be used for each test to account for multiple comparisons.

Power and sample size

Power for the study was estimated by simulation based on test scores of patients with severe TBI participating in a clinical trial of magnesium sulfate conducted at the University of Washington (Temkin et al., 2007). Since many of the neuropsychological tests are not identical for the Spanish-speaking subjects in this study and the English-speaking subjects in the magnesium study, tests of similar constructs were used in the simulation. For example, scores on Selective Reminding sum of recall (Buschke, 1973) were used in the simulation instead of the Spanish Verbal Learning test (Artiola-i-Fortuny et al., 1999) used in the trial, as both are verbal list-learning tasks. A sample size of 324 (162 per group) gives 80% power to detect a difference of 10 percentage points (e.g., from 50% to 60% favorable outcome) in the percent with good or moderate recovery on the GOS, and similar improvement on the other measures. We defined similar improvement as the same change in log odds for categorical outcomes, and the same reduction in deficit for continuous outcomes.

Results

As of August 2010, we have entered 176 participants into the trial, 58% of all eligible patients who were screened. For those eligible and not entered, 63 did not have a relative present to consent, for 43 there were no beds available, 15 refused consent, there was no monitor or catheter available for 5, and the reason for 1 is unknown. Baseline characteristics of 159 randomized participants for whom data collection was complete on 8/31/10, are presented in Table 2.

Current enrollment is 81% of that expected to date. The follow-up rate at 6 months is 87%. Based on the current

TABLE 2. PARTICIPANT DEMOGRAPHICS

Name of hospital n	Japones n=42	San Juan Dios n=55	Viedma n=45	Tarija n=17	Overall n=159	p Value
Age (mean ± SD)	31.0 ± 12.3	31.5 ± 15.1	35.4 ± 14.6	42.7 ± 19.0	33.6 ± 15.1	0.040 ^a
Sex						0.910 ^b
Female	5 (12%)	5 (9%)	6 (14%)	2 (12%)	18 (11%)	
Male	37 (88%)	50 (91%)	38 (86%)	15 (88%)	140 (89%)	
Unknown	0	0	1	0	1	
Race						<0.001 ^b
Caucasian	0 (0%)	2 (4%)	5 (11%)	5 (29%)	12 (8%)	
African-American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Hawaiian/Pacific-Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
American Indian	1 (2%)	5 (9%)	7 (16%)	5 (29%)	18 (11%)	
Mixed (primarily indigenous and Caucasian)	41 (98%)	48 (87%)	32 (73%)	7 (41%)	128 (81%)	
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Unknown	0	0	1	0	1	
Years of education (mean ± SD)	10.0 ± 4.3	9.3 ± 4.7	8.6 ± 5.1	5.8 ± 3.3	8.9 ± 4.7	0.015*
Cause of injury						0.001 ^b
Motor vehicle accident	6 (14%)	8 (15%)	8 (18%)	1 (6%)	23 (14%)	
Motorcycle accident	21 (50%)	22 (40%)	12 (27%)	2 (12%)	57 (36%)	
Bicycle accident	2 (5%)	0 (0%)	1 (2%)	4 (24%)	7 (4%)	
Pedestrian accident	9 (21%)	10 (18%)	10 (22%)	2 (12%)	31 (19%)	
Fall from a height	3 (7%)	8 (15%)	8 (18%)	1 (6%)	20 (13%)	
Fall	0 (0%)	1 (2%)	2 (4%)	2 (12%)	5 (3%)	
Robbery/assault	1 (2%)	5 (9%)	4 (9%)	2 (12%)	12 (8%)	
Accidental blow by object	0 (0%)	1 (2%)	0 (0%)	1 (6%)	2 (1%)	
Other	0 (0%)	0 (0%)	0 (0%)	1 (6%)	1 (1%)	
Unknown	0	0	0	1	1	
Glasgow Coma Scale score^c						0.027 ^b
GCS 3–5 (or motor 1–2 if intubated)	6 (14%)	13 (24%)	12 (27%)	9 (53%)	40 (25%)	
GCS 6–8 (or motor 3–5 if intubated)	36 (86%)	42 (76%)	33 (73%)	8 (47%)	119 (75%)	
AIS head (mean ± SD)	3.6 ± 0.8	4.2 ± 0.6	4.2 ± 0.9	3.9 ± 0.9	4.0 ± 0.8	0.001*

*Significance by analysis of variance.

^aSignificance by analysis of variance (log-transformed values).^bSignificance by Fisher exact test.^cUsing the post-admission GCS score or otherwise the admission GCS score (pro-rated if patient is intubated).

AIS, Abbreviated Injury Scale; SD, standard deviation.

enrollment rate and the addition of centers, the trial is expected to reach its enrollment goal of 324 participants by September of 2011.

Discussion

In the chapter on indications for ICP monitoring, the “Guidelines for the Management of Severe Traumatic Brain Injury” states: “A randomized clinical trial (RCT) of ICP monitoring...would be extremely useful...but it is unlikely, considering that most TBI experts consider ICP or CPP parameters to be the primary basis for ICU management decisions in the care of the severe TBI patient” (Bratton et al., 2007). Statements to this effect have also appeared elsewhere (Bullock et al., 1996; Chesnut, 1995; Cremer et al., 2005; Shafi et al., 2008), reflecting the recognized paucity of rigorous literature support for current concepts and methods of using ICP monitoring. In spite of the lack evidence, such management approaches are so widely accepted that investigators are not comfortable managing a study control group without ICP monitoring. Even publications that question the efficacy of

monitor-based ICP therapy reflect this lack of comfort (Cremer et al., 2005; O’Brien, 1984; Shafi et al., 2008). Thus, ICP monitoring in HICs and some LMICs has acquired the status of “standard of care,” without being subjected to the same level of preliminary investigation considered necessary when introducing a new drug or intervention.

In Latin America, although trauma centers are profoundly influenced by their countries’ economic status, many ICUs are generally adequately equipped to perform excellent intensive care management of severe TBI patients, although the care given is certainly basic. In addition, it has been our experience that the intensivists in Latin America are as current, or more so, in terms of the literature as their colleagues in HICs. Thus, this environment consisted of the components necessary and sufficient to test the efficacy of ICP monitoring in an ethically sound manner: (1) highly skilled and educated clinicians; (2) rigorous, protocol-driven ICUs; (3) an absence of monitors as standard-of-care; and (4) the presence of equipoise.

While the design of an RCT is relatively straightforward, the actual execution is vulnerable to bias and confounding at

multiple junctures. This is true globally, and is of particular concern in clinical environments that are at the beginning stages of creating a research culture. As stated earlier, the team was already trained and experienced in the basic concepts of conducting a good study, including representative samples, adequate random assignment, allocation concealment and outcome assessment blinding, high follow-up rate, and attention to the multiple means of incurring measurement error. A subset of the key investigators was formally trained in clinical research, including Master Degree and year-long certificate programs, and clinical research rotations. Data quality was managed by checking the accuracy of every data point and tallying errors until the rate was at an acceptable level, and is being 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 work on problems together, and to foster team spirit and individual ownership and responsibility. The efforts have produced concrete results, such as data error rates below 1%, and a follow-up rate of 87%. Further, these results demonstrate the ability of Latin American and U.S. investigators to work together successfully as part of a consortium to conduct rigorous multi-center clinical trials addressing critical health care problems in a complex, multi-national setting.

The long-term goal of the NTRG is to establish a TBI literature base in Latin America that is specific to those countries' patients, from which evidence-based guidelines can be generated. This trial is a step toward realizing that goal. The purpose of this article is to introduce the study to the international neurocritical care community. Future publications will include detailed descriptions of implementation, analyses of recruitment challenges, and of course, the outcome analyses.

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Author Disclosure Statement

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