will demand that all the primary data be made public, along with the analytical tools necessary to reanalyze, test, refine, and build on them. Data security will have to evolve and thereby win the public's trust with new techniques that will do what now seems impossible: guarantee protection of privacy while providing detailed information about each person. Societies will come to accept that comprehensive knowledge of disease, prevention, and effective treatment is an essential public good.

Biomedical research, data technologies, and clinical care all require resources, but the era of shifting more and more economic resources toward health care is going to end. The medicine of the future will focus on more efficient use of resources to prevent disease, with the goal of delivering what provides the best value for the patient who needs treatment. The future of medicine also depends on reducing the enormous disparities in health, particularly those between the richest and the poorest countries of the world. A basic standard of sound medical care will become an expectation of every society. Research-rich countries may come to see that achieving basic health care throughout the world is a strategy to promote stability and peace. The increasing power of information and communication technologies can help find ways to improve global health. However, that goal also requires the educational and economic development that are essential for societies to achieve a reasonable standard of health. The moral mandate here only becomes stronger as clinical progress continues to accelerate in developed societies.

The high-technology, information-rich medicine of the future will provide powerful and useful tools for clinical medicine. The medicine of the future will not, of course, solve all problems, and it cannot prevent violent or self-destructive human behaviors. Patients will continue to rely on physicians and the medical community for the guidance, support, and help that only a skilled and caring heath professional can deliver. The medical community must provide direction to ensure that powerful new technologies are used to benefit the health of all. As advances in science and technology continue to bring disruptive changes, the *Journal* must continue to evolve creatively in order to continue in its mission of inspiring discovery and advancing care. As we head into this medicine of the future, the *Journal* should remain true to the principles that were set down by its founding physicians two centuries ago: "The *Journal* will always be open to the accurate observer of nature, the useful experimenter, and the rational therapist."[3]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From Boston Children's Hospital and Harvard Medical School — both in Boston (I.S.K.).

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Brain in a Box

Allan H. Ropper, M.D.

The brain, despite its sophistication, resides in a rudimentary container. The rigid cranium restricts enlargement of its contents, so that intracranial pressure rises rapidly as brain volume expands. When pressure becomes greatly elevated, cerebral blood flow is impeded, and the result is brain death. For this reason, the reduction of elevated intracranial pressure is a central theme in the management of traumatic brain injury, cerebral hemorrhage, and most other intracranial mass lesions. The widely adopted recommendation of the Brain Trauma Foundation is to keep intracranial pressure below 20 mm Hg in order to avoid poor outcome[1]; adherence requires that the pressure be measured directly. This advice and the assumptions that underlie it are tested in the report by Chesnut and colleagues in the *Journal*.[2] They compared therapy based on the measurement of intracranial pressure with a treatment regimen that was regulated more simply with the use of clinical observation and computed tomographic scans; the outcomes were the same.

Physiological measurements are inherently more appealing than clinical signs because they give the impression of precision and of proximity to disease. Foremost among these measurements has been pulmonary-capillary wedge pressure. A totem for 40 years, wedge pressure has been shown in the past decade to be relatively ineffective in guiding the treatment of congestive heart failure,[3] high-risk surgical patients,[4] and septic shock.[5] The article by Chesnut et al. questions a similar notion, also closely held, that monitoring intracranial pressure to direct treatment improves outcome.

The objections to the trial are easily anticipated. Skeptics will express concern about its locale, South America, particularly because practices used in the intensive care unit (ICU) and aftercare may not be similar to those used in North America and Europe. A second reservation regards the devices used to measure pressure. Unlike the external ventricular drains used in many ICUs, which allow drainage of spinal fluid to reduce pressure, the intraparenchymal monitors used in the trial do not have that advantage. But this technical difference is not enough to negate the conclusions of the study, since the measurements produced by each method are reasonably close. Third, the composite end point in the trial was contrived, but mortality at 14 and 30 days was similar whether intracranial pressure was monitored or not, a finding that supports the conclusion that measurement makes little difference in terms of reducing the early damage caused by elevated intracranial pressure.

Finally, the argument could be made that the level of pressure selected to trigger treatment was too low (similar misgivings arose with regard to another study recently published in the *Journal* that investigated the efficacy of bilateral decompressive craniectomy in patients with head injury[6]). It may seem counterintuitive to object to the idea of initiating treatment at the lowest possible pressure, since this strategy should anticipate and prevent problems that would occur at higher pressures. However, the opportunity to change the outcome of catastrophic illness is limited. Patients with moderate brain trauma may do well without treatment, and the outcome in severely injured patients with very high pressures and diffuse cerebral injury may be unalterable. Consequently, the selection of a pressure of 20 mm Hg, taken from arbitrary guidelines, to prompt initiation of treatment may not be appropriate.

There may be a larger conceptual problem that pervades the field of traumatic brain injury. In this study, as well as in the study of decompressive craniectomy, all efforts were directed at lowering the average pressure within the cranium, but clinical outcome in survivors partly reflects the specific area of compression, notably, the upper midbrain, thalamus, and reticular activating system. Damage to these deep regions of the brain is the result of mechanical tissue displacement, not the summated pressure that is distributed throughout the brain. Intracranial pressure and brain-stem compression can be viewed as parallel but disparate indicators of the effects of an intracranial mass. Treating one does not consistently improve the other.

Chesnut and colleagues do not advocate abandoning the treatment of elevated intracranial pressure any more than the authors of studies on wedge pressure reject the administration of fluid boluses in the treatment of shock. Their study does expose misconceptions about intracranial pressure.

We are still likely to continue to doubt clinical signs, which indeed do not reflect global pressure inside the cranium, but stupor, coma, posturing, and dilatation of the pupils indicate compression of the midbrain, and according to this study they are very suitable observations to use in directing treatment. Furthermore, if the neurologic examination is obscured by paralysis and sedation, which are frequently induced in the ICU, measuring intracranial pressure remains a valid approach. In the future there may be other means of detecting early compression of the brain stem. Until then, clinical methods are fine.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Department of Neurology, Brigham and Women's Hospital, Boston.

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Trials in Kidney Disease — Time to EVOLVE

Vlado Perkovic, M.B., B.S., Ph.D., and Bruce Neal, M.B., Ch.B., Ph.D.

Patients with kidney disease face a substantially increased risk of cardiovascular events and death[1] — one in five patients who are undergoing dialysis die each year in the United States.[2] Elevated parathyroid hormone levels are almost universal in persons with advanced kidney failure and have been associated with these risks.[3] Cinacalcet is an oral calcimimetic agent approved by the Food and Drug Administration (FDA) in 2004 for the treatment of secondary hyperparathyroidism in patients with dialysis-dependent kidney failure. Early reports[4,5] supported the possibility that cinacalcet conferred cardiovascular protection and reduced fracture risk, although the statistical power of these studies was limited.

In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, now reported in the *Journal*, Chertow et al.[6] tested the hypothesis that cinacalcet, as compared with placebo, would reduce the risk of death and cardiovascular events in dialysis-dependent patients with hyperparathyroidism. The trial enrolled 3883 participants from many countries and followed them for up to 5 years.

Among patients in the cinacalcet group, the nonsignificant relative reduction in the primary outcome of 7% (odds ratio, 0.93; 95% confidence interval, 0.85 to 1.02) was disappointing, particularly given the huge effort involved in conducting the study. It is also disappointing that a number of prespecified secondary analyses hint that the trial may have missed the detection of a real benefit. Thus, the results point to a missed opportunity to identify or exclude a protective therapy for patients undergoing dialysis.

No clear effect on fracture was identified, although a reduced risk of calciphylaxis was observed, with low overall rates in both groups (6 vs. 18 events, $P=0.009$). The need for parathyroidectomy was also reduced, although this finding is a matter of indeterminate importance. The substantially elevated risk of adverse events in the cinacalcet group, including an increased number of neoplastic events, is a cause for concern that requires further analysis.

Why was the primary result of the trial negative? The surprising imbalance in baseline characteristics between the two groups may well have had an effect — and probably represents simple bad luck but illustrates the importance of stratification for key prognostic factors. More important were the high rates of treatment crossover during the trial: almost two thirds of patients in the cinacalcet group discontinued active therapy, and one fifth of those in the placebo group started taking commercially available cinacalcet before trial completion. The resultant reduction in the between-group separation in parathyroid hormone levels substantially reduced the power of the trial to test its hypotheses.

The main reasons for early therapy discontinuation were adverse events (18.1% in the cinacalcet group and 13.0% in the placebo group) and administrative decisions or patient requests (21% and 31%, respectively). These rates highlight the challenges of maintaining the involvement of both site investigators and study participants who have multiple coexisting conditions in a long-term trial, suggesting that better models are required.

The large proportion of patients in the placebo group who started taking commercially available cinacalcet is also striking, since although the drug had been approved for use, there has been no clearly demonstrated benefit for patient-level outcomes.[4] A regulatory process that allowed the agent to be registered and widely used without stronger evidence of efficacy suggests a system failure. It is even more troubling that this system also had a serious effect on the capacity of the EVOLVE trial to define the effects of the drug on definitive clinical outcomes.

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A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

Randall M. Chesnut, M.D., Nancy Temkin, Ph.D., Nancy Carney, Ph.D., Sureyya Dikmen, Ph.D., Carlos Rondina, M.D., Walter Videtta, M.D., Gustavo Petroni, M.D., Silvia Lujan, M.D., Jim Pridgeon, M.H.A., Jason Barber, M.S., Joan Machamer, M.A., Kelley Chaddock, B.A., Juanita M. Celix, M.D., Marianna Cherner, Ph.D., and Terence Hendrix, B.A.

ABSTRACT

BACKGROUND

Intracranial-pressure monitoring is considered the standard of care for severe traumatic brain injury and is used frequently, but the efficacy of treatment based on monitoring in improving the outcome has not been rigorously assessed.

METHODS

We conducted a multicenter, controlled trial in which 324 patients 13 years of age or older who had severe traumatic brain injury and were being treated in intensive care units (ICUs) in Bolivia or Ecuador were randomly assigned to one of two specific protocols: guidelines-based management in which a protocol for monitoring intraparenchymal intracranial pressure was used (pressure-monitoring group) or a protocol in which treatment was based on imaging and clinical examination (imaging–clinical examination group). The primary outcome was a composite of survival time, impaired consciousness, and functional status at 3 months and 6 months and neuropsychological status at 6 months; neuropsychological status was assessed by an examiner who was unaware of protocol assignment. This composite measure was based on performance across 21 measures of functional and cognitive status and calculated as a percentile (with 0 indicating the worst performance, and 100 the best performance).

RESULTS

There was no significant between-group difference in the primary outcome, a composite measure based on percentile performance across 21 measures of functional and cognitive status (score, 56 in the pressure-monitoring group vs. 53 in the imaging–clinical examination group; P=0.49). Six-month mortality was 39% in the pressure-monitoring group and 41% in the imaging–clinical examination group (P=0.60). The median length of stay in the ICU was similar in the two groups (12 days in the pressure-monitoring group and 9 days in the imaging–clinical examination group; P=0.25), although the number of days of brain-specific treatments (e.g., administration of hyperosmolar fluids and the use of hyperventilation) in the ICU was higher in the imaging–clinical examination group than in the pressure-monitoring group (4.8 vs. 3.4, P=0.002). The distribution of serious adverse events was similar in the two groups.

CONCLUSIONS

For patients with severe traumatic brain injury, care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT01068522.)

From the Departments of Neurological Surgery (R.M.C., N.T., S.D., J.P., J.B., K.C., J.M.C.), Orthopaedics and Sports Medicine (R.M.C.), Biostatistics (N.T.), and Rehabilitation Medicine (S.D., J.M.), University of Washington, Harborview Medical Center, Seattle; the Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland (N.C.); Hospital de Emergencias Dr. Clemente Alvarez, Santa Fe (C.R., G.P., S.L.), and Hospital Nacional Professor Alejandro Posadas, Buenos Aires (W.V.) — both in Argentina; and the Departments of Psychiatry (M.C.) and HIV Neurobehavioral Research Programs (T.H.), University of California, San Diego, La Jolla. Address reprint requests to Dr. Chesnut at the University of Washington, Harborview Medical Center, Department of Neurological Surgery, 325 Ninth Ave., Box 359766, Seattle, WA 98104, or at chesnutr@uw.edu.

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Although the monitoring of intracranial pressure is widely recognized as standard care for patients with severe traumatic brain injury, its use in guiding therapy has incomplete acceptance, even in high-income countries.[1-3] Successive editions of the guidelines for the management of severe traumatic brain injury[4-7] have documented the inadequate evidence of efficacy, calling for randomized, controlled trials while also noting the ethical issues that would be posed if the control group consisted of patients who did not undergo monitoring. The identification of a group of intensivists in Latin America who routinely managed severe traumatic brain injury without using available monitors and for whom there was equipoise regarding its efficacy eliminated that ethical constraint and led to the implementation of the randomized, controlled trial described here.

Data from rigorous randomized, controlled trials of intracranial-pressure monitoring in the management of traumatic brain injury are lacking, and few high-quality, prospective case–control or cohort studies have been conducted.[7] Historically, the use of monitoring-based management has been confounded by several factors. These include the involvement of intensivists and the development of the subspecialty of neurocritical care; the vast improvements in the resuscitation of patients with trauma (and those with brain injury, in particular); myriad developments in the management of traumatic brain injury during prehospital emergency care, emergency department care, and rehabilitation; and marked improvements in monitoring and management techniques in the intensive care unit (ICU). Such confounding can be rigorously addressed only in a randomized, controlled trial. Here we report the results of such a trial.

The primary objective of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial was to determine whether the information derived from the monitoring of intracranial pressure in patients with severe traumatic brain injury improves medical practice and patient outcomes. Our primary hypothesis was that a management protocol based on the use of intracranial-pressure monitoring would result in reduced mortality and improved neuropsychological and functional recovery at 6 months. Our secondary hypothesis was that incorporating intracranial-pressure monitoring into the management of severe traumatic brain injury would have benefits for the health care system, including a reduced risk of complications and a shorter ICU stay.

Methods

Study Design

The study was a multicenter, parallel-group trial, with randomized assignment to intracranial-pressure monitoring (the pressure-monitoring group) or imaging and clinical examination (the imaging–clinical examination group). Randomization was stratified according to study site, severity of injury, and age. The study was started at three Bolivian hospitals (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org); an additional Bolivian hospital and two Ecuadorian hospitals were subsequently recruited to increase enrollment. All six sites had ICUs staffed with intensivists, 24-hour computed tomographic (CT) services and neurosurgery coverage, and high volumes of patients with trauma.

Eligibility

All patients presenting with traumatic brain injury were screened for eligibility on admission at the study hospitals. To be included in the study, patients had to be 13 years of age or older and have a score on the Glasgow Coma Scale (GCS) of 3 to 8 (with a score on the GCS motor component of 1 to 5 if the patient was intubated) or a higher score on admission that dropped to the specified range within 48 hours after injury. (The GCS ranges from 3 to 15, with higher scores indicating higher levels of consciousness; the motor score ranges from 1 to 6.) Patients with a GCS score of 3 and bilateral fixed and dilated pupils and those with an injury believed to be unsurvivable were excluded. The complete list of inclusion and exclusion criteria has been reported previously[8] and is available in the Supplementary Appendix. Informed consent was obtained for all participants.

Group Assignments and Interventions

Randomization sequences were computer-generated by a data-center biostatistician and were stratified according to site, severity of injury (GCS score of 3 to 5, or GCS motor score of 1 to 2 if the patient was intubated, vs. GCS score of

6 to 8, or GCS motor score of 3 to 5 if the patient was intubated), and age (<40 years vs. ≥40 years), with a block size of 2 or 4 (see the Supplementary Appendix).

The study was conducted in accordance with the protocol (available at NEJM.org), which specified that three CT scans be obtained (at baseline, 48 hours, and 5 to 7 days) and standard supportive care provided for each patient, with care to include mechanical ventilation, sedation, and analgesia. Non-neurologic problems were managed aggressively in both groups.

Patients randomly assigned to the pressure-monitoring group had an intraparenchymal monitor placed as soon as possible and were treated to maintain an intracranial pressure of less than 20 mm Hg, in accordance with the guidelines for the management of severe traumatic brain injury[4-7] (for more information see the description of treatment protocols in the Supplementary Appendix). Drainage of cerebrospinal fluid required ventriculostomy placement. The care for patients randomly assigned to the imaging–clinical examination group was provided in accordance with a protocol based on the pretrial standard for care at the three original participating hospitals (see the Supplementary Appendix). In the absence of intracranial mass lesions requiring surgery, signs of intracranial hypertension on imaging or clinical examination were treated first with hyperosmolar therapies with the use of protocol-specified doses on a fixed schedule of administration, optional mild hyperventilation (at a partial pressure of arterial carbon dioxide of 30 to 35 mm Hg), and optional ventricular drainage. Continuing edema prompted consideration of the administration of high-dose barbiturates. Additional treatments were required for patients with "neuroworsening,"[9] persistent edema, or clinical signs of intracranial hypertension. (More information on the interventions provided and on operational definitions — including the definition of neuroworsening — is available in the Supplementary Appendix.)

OUTCOMES

The primary outcome, assessed within 6 months after the study onset, was a composite of 21 components: measures of survival (survival time, counted as 1 component), duration and level of impaired consciousness (time to follow commands, sum of errors on the orientation questions from the Galveston Orientation and Amnesia Test [GOAT] on discharge from the hospital — 2 components), functional status and orientation 3 months after injury (assessed with the use of the Extended Glasgow Outcome Scale [GOS-E], the Disability Rating Scale, and GOAT — 3 components), and functional and neuropsychological status 6 months after injury (15 components). The battery of tests included measures of mental status, working memory, information-processing speed, episodic memory and learning, verbal fluency, executive function, and motor dexterity (information on the range and direction of scores for each measure is provided in Table S2 in the Supplementary Appendix). Trained examiners who were unaware of the group assignments administered the tests at 3 and 6 months. Data quality and monitoring are discussed in the Supplementary Appendix.

For the primary outcome, each participant's percentile was determined separately for each of the 21 measures; the overall outcome was the average of the 21 percentiles[10] (on a scale from 0 to 100, with lower percentiles representing worse outcomes); for details, see the outcomes section in the Supplementary Appendix. Protocol-specified secondary outcomes were the length of stay in the ICU (measured as the total number of days in the ICU and the number of days in the ICU on which the patient received at least one brain-specific treatment) and systemic complications. Brain-specific treatments were those directed at intracranial hypertension and included the administration of hyperosmolar agents and pressors and the use of hyperventilation but excluded ventilation, sedation, and analgesia. Additional, post hoc secondary outcomes were the hospital length of stay, the number of days of mechanical ventilation, treatment with high-dose barbiturates or decompressive craniectomy, and therapeutic intensity (for details, see the Supplementary Appendix). For some analyses focused specifically on interventions for intracranial hypertension, we defined the duration of therapy as the number of days from injury until the last brain-specific treatment. Data for patients who survived for more than 1 day after the last brain-specific treatment (collectively referred to as the brain-treatment survivors subgroup) were also analyzed. We integrated brain-specific treatments by summing the number of treatments delivered per hour over the course of the treatment interval.

STUDY OVERSIGHT

The study was approved by the institutional review board at the University of Washington and the ethics committees at all study centers. All authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol. Integra Life Sciences donated the catheters used in monitoring intracranial pressure and provided additional unrestricted support for this project. Integra had no role in the design or conduct of the study, the data analysis, or the writing of the manuscript.

STATISTICAL ANALYSIS

The planned sample size of 324 was determined by means of simulation to provide 80% power to detect an increase of 10 percentage points in the percentage of patients with a good outcome or with moderate disability according to the GOS-E (odds ratio with imaging and clinical examination vs. pressure monitoring, 1.5), and a corresponding improvement on other measures (see the Supplementary Appendix). One planned interim efficacy analysis was conducted when half the participants had undergone the 6-month assessment.

The primary hypothesis was tested with the use of the blocked Wilcoxon test,[11] with blocking on stratification factors, and a two-sided significance level of 0.05. We obtained odds ratios and confidence intervals from a logistic proportional-odds model, accounting for the same factors (see the Supplementary Appendix).[10] This analysis was supplemented by similar analyses of individual measures and composite analyses of subgroup measures. Cox models were used to analyze survival. A significance level of 0.01 was used to test secondary hypotheses. The main analyses included data on all participants randomly assigned to a treatment group (intention-to-treat population). Sensitivity analyses included analyses restricted to patients who survived, those who received the assigned treatment, and those who survived for at least 24 hours after receiving brain-specific treatments.

RESULTS

STUDY PARTICIPANTS

Patients were recruited between September 2008 and October 2011, with the last follow-up visit occurring in May 2012 (see Fig. S1 in the Supplementary Appendix for information on screening, randomization, and follow-up). The trial ended when the planned sample size was attained. Of 528 eligible patients, 204 (39%) were excluded before randomization (see Table S4 in the Supplementary Appendix for a comparison of the baseline characteristics of enrolled patients and excluded patients). Of the patients who underwent randomization, 92% were followed for 6 months or until death (Table S4 in the Supplementary Appendix). Protocol violations were few (Table S5 in the Supplementary Appendix). The two treatment groups were similar at baseline with regard to all baseline characteristics (Table 1, and Table S6 in the Supplementary Appendix).

Traffic incidents were the primary cause of injury. Only 45% of participants were transported to the first hospital by ambulance. Most were transferred to study hospitals from another center; the median time to arrival at the first hospital was 1.0 hour for direct admissions and 2.7 hours for transfers. The median time from injury to arrival at study centers for all patients was 3.1 hours. We were unable to acquire accurate information on prehospital interventions or early secondary insults (i.e., hypoxemia or hypotension) because they were not uniformly assessed and recorded.

INITIAL INJURY

Of the study participants who underwent randomization, 24% had a GCS score that was higher on admission but subsequently dropped to the specified range for enrollment. The median GCS motor score at randomization was 4.0; 49% of participants had localizing brain injuries, with none of the participants following commands. One or both pupils were nonreactive in 44% of participants. On the Abbreviated Injury Scale (ranging from 0 to 6, with higher scores indicating more severe injury), the median score for head injury was 5; 82% of participants had a score of 4 or higher. Initial CT revealed a high severity of injury overall, with grade III diffuse injury[2-14] (swelling of the brain causing compression of the basal cisterns, without a mass lesion or a midline shift of >5 mm) in 43% of the participants and mass lesions requiring surgical treatment in 33%. Mesencephalic cisterns were compressed or absent in 85% of the participants, and the midline was shifted by more than 5 mm in 36%.

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Pressure-Monitoring Group (N = 157)	Imaging–Clinical Examination Group (N = 167)
Age — yr		
Median	29	29
Interquartile range	22–44	22–44
Male sex — no. (%)	143 (91)	140 (84)
Transferred from another hospital — no./total no. (%)	97/157 (62)	101/166 (61)
Time to admission to study hospital — hr		
Median	3.5	2.9
Interquartile range	1.1–8.3	1.0–6.5
Direct admissions		
Median	1.0	1.0
Interquartile range	0.5–1.5	0.5–2.0
Transfers		
Median	6.3	5.0
Interquartile range	3.3–12.2	2.8–9.8
Time to admission to first hospital		
Median	3.0	2.5
Interquartile range	1.1–6.6	1.3–6.3
Glasgow Coma Scale at randomization — motor score†		
Median	5	4
Interquartile range	3–5	3–5
Marshall classification on initial CT — no. (%)‡		
Diffuse injury I	1 (1)	0
Diffuse injury II	24 (15)	20 (12)
Diffuse injury III	70 (45)	68 (41)
Diffuse injury IV	10 (6)	12 (7)
Evacuated mass lesion	48 (31)	58 (35)
Nonevacuated mass lesion	4 (3)	7 (4)
Abbreviated Injury Scale — score for head§		
Median	5	5
Interquartile range	4–5	4–5
Mesencephalic cisterns compressed or absent on initial CT — no./total no. (%)	131/157 (83)	143/165 (87)
Midline shift (≥5 mm) detected on initial CT — no./total no. (%)	53/157 (34)	64/164 (39)
Signs of intracranial hypertension detected on initial CT — no./total no. (%)¶	140/156 (90)	146/164 (89)

* There were no significant differences between the groups. Additional data are available in Table S6 in the Supplementary Appendix.

† The range of scores for the motor component of the Glasgow Coma Scale is 1 to 6, with higher scores indicating a higher level of consciousness.

‡ The Marshall classification of traumatic brain injury is based on a review of CT scans, with diffuse injury I indicating no visible pathology, diffuse injury II indicating the presence of cisterns, with a midline shift of 0 to 5 mm, diffuse injury III indicating pathology similar to that in diffuse injury II, but with swelling, and diffuse injury IV indicating pathology similar to that seen in diffuse injuries II or III, with a midline shift of more than 5 mm. For more detailed information see the Definitions section in the Supplementary Appendix and Marshall et al.[12] Percentages for this variable exclude unknown values.

§ Scores on the Abbreviated Injury Scale range from 1 to 6, with higher values representing more severe injury.

¶ Data on signs of intracranial hypertension are based on the impression of the interpreting physician.

CLINICAL OUTCOMES

Table 2 (and Table S7A in the Supplementary Appendix) shows the results for the primary (composite) outcome, individual measures, and sensitivity analyses. There were no significant differences between groups. The survival rates for the two study groups are shown in Figure 1. The 14-day mortality was 30% in the imaging–clinical examination group as compared with 21% in the pressure-monitoring group (hazard ratio, 1.36; 95% confidence interval [CI], 0.87 to 2.11; P=0.18); the 6-month mortality was 41% and 39% in the two groups, respectively (hazard ratio, 1.10; 95% CI, 0.77 to 1.57; P=0.60). The results for the primary outcome were similar in an analysis restricted to survivors and in analyses of subgroups defined by sex (prespecified subgroup analysis), site, CT findings, and age (Tables S7B and S8 in the Supplementary Appendix).

PROCESSES OF CARE

Table 3 (and Table S9A in the Supplementary Appendix) shows the between-group comparisons for variables reflecting processes of care. The hospital length of stay was marginally shorter in the imaging–clinical examination group than in the pressure-monitoring group only when all participants who underwent randomization were included in the analysis. There were no significant differences between groups with respect to the ICU length of stay, in either the intention-to-treat population or the brain-treatment survivors subgroup (Table S9B in the Supplementary Appendix). For this subgroup, the median length of stay was 13 days in the ICU and 26 days in the hospital. There were no significant between-group differences in the number of days of mechanical ventilation. The evaluation of non-neurologic complications also revealed no significant differ-

Table 2. Clinical Outcomes.*

Variable	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value	Proportional Odds Ratio (95% CI)†
Patients assessed at 6 mo — no. (%)	144 (92)	153 (92)		
Primary outcome‡			0.49§	1.09 (0.74–1.58)
Median	56	53		
Interquartile range	22–77	21–76		
Cumulative mortality at 6 mo — %	39	41	0.60¶	1.10 (0.77–1.57)
GOS-E scale at 6 mo — no. (%)‖				
Death	56 (39)	67 (44)**	0.40§	1.23 (0.77–1.96)
Unfavorable outcome	24 (17)	26 (17)		
Favorable outcome	63 (44)	60 (39)		

* Additional outcomes are listed in Table S7A in the Supplementary Appendix. Outcomes for survivors only are in listed Table S7B in the Supplementary Appendix.

† Proportional odds ratios were adjusted for site, age, and severity of injury. A value of more than 1 indicates a better outcome for the pressure-monitoring group. The study was designed to detect a difference corresponding to an odds ratio of 1.5. CI denotes confidence interval.

‡ The primary outcome was based on a composite measure and calculated as an average percentile over 21 elements. The range is 0 to 100, and a higher percentile indicates a better outcome. A detailed description of the composite outcome appears in the outcomes section in the Supplementary Appendix; individual elements are listed in Table S2 in the Supplementary Appendix.

§ Statistical significance was determined by means of a blocked Wilcoxon test stratified according to site, age, and severity of injury at randomization.

¶ Statistical significance was determined by means of Cox model regression with adjustment for site, age, and severity of injury at randomization.

‖ The Extended Glasgow Outcome Scale (GOS-E) ranges from 1 to 8, with 1 indicating death and 8 indicating the most favorable recovery. Patients with scores ranging from 2 to 4 were classified as having an unfavorable outcome, and those with scores ranging from 5 to 8 were classified as having a favorable outcome.

** Mortality for the 6-month GOS-E assessment was higher than cumulative mortality because data for participants who were lost to follow-up were excluded from the 6-month GOS-E assessment but were included as censored data for the calculation of cumulative mortality.

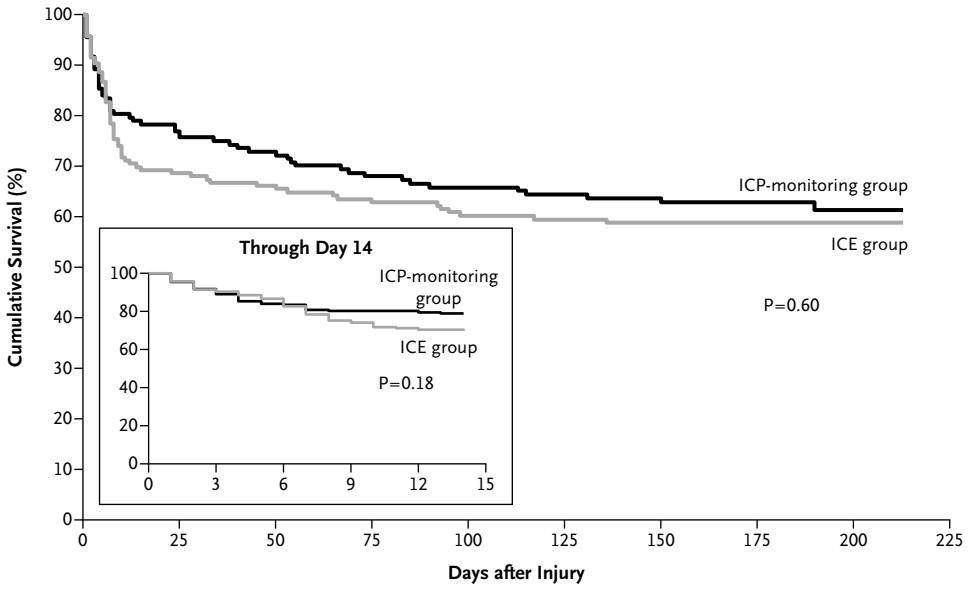

Figure 1. Cumulative Survival Rate According to Study Group.

A Kaplan–Meier survival plot based on the prespecified analysis shows the cumulative survival rate at 6 months among patients assigned to imaging and clinical examination (ICE) as compared with those assigned to intracranial-pressure (ICP) monitoring (hazard ratio for death, 1.10; 95% confidence interval [CI], 0.77 to 1.57). The inset shows the results of the post hoc analysis at 14 days (hazard ratio, 1.36; 95% CI, 0.87 to 2.11).

ences between treatment groups, except that patients in the pressure-monitoring group had a significantly higher rate of decubitus ulcers (12%, vs. 5% in the imaging–clinical examination group; P=0.03).

The median time during which intracranial pressure was monitored was 3.6 days in the entire pressure-monitoring group and 4.0 days in the brain-treatment survivors subgroup (Table 3, and Tables S9A and S9B in the Supplementary Appendix). The median and mean percentages of readings that were 20 mm Hg or higher were 7 and 20%, respectively, in the entire study population and 5 and 13%, respectively, in the brain-treatment survivors subgroup. For these respective groups, the intracranial pressure was 20 mm Hg or higher initially in 37% and 29% of patients and at any time during monitoring in 79% and 76% of patients. The incidence of neuroworsening after randomization was 25% for the entire study population and did not differ significantly between the two treatment groups.

The median interval during which patients received brain-specific treatment was significantly longer in the imaging–clinical examination group than in the pressure-monitoring group. In addition, post hoc analyses of integrated treatment intensity (see the definition in the outcomes section in the Supplementary Appendix) revealed that the total number of treatments was significantly greater for the imaging–clinical examination group as a whole and for the brain-treatment survivors subgroup than for the pressure-monitoring group. Table 3, and Table S9A in the Supplementary Appendix, show that the use of high-dose barbiturates was greater in the pressure-monitoring group than in the imaging–clinical examination group (24% vs. 13%). There was no significant between-group difference in the number of patients who underwent craniectomy. The proportion of patients treated with hypertonic saline and the proportion treated with hyperventilation were significantly higher in the imaging–clinical examination group than in the pressure-monitoring group (72% vs. 58% and 73% vs. 60%, respectively). Among patients who received treatment with mannitol or hypertonic saline, the duration of treatment was longer in the imaging–clinical evaluation group than in the pressure-monitoring group (21 hours vs. 13 hours for

mannitol and 21 hours vs. 10 hours for hypertonic saline).

ADVERSE EVENTS

The distributions of serious adverse events, adverse events, complications, and catheter-related adverse events are shown in Table 4, as well as in Tables S10A and S10B in the Supplementary Appendix. There were no serious catheter-related adverse events in either study group.

DISCUSSION

Our results do not support the hypothesized superiority of management guided by intracranial-pressure monitoring over management guided by neurologic examination and serial CT imaging in patients with severe traumatic brain injury. Intracranial-pressure monitoring is the cornerstone of treatment for severe traumatic brain injury. The principle guiding additional interventions, such as the monitoring of cerebral perfusion pressure or tissue-perfusion modification, is the maintenance of intracranial pressure below 20 mm Hg.

Most of the data from nonrandomized, controlled trials support the association of treatment based on monitored intracranial pressure with improved recovery, which has led to the recommendation of this approach in successive editions of published guidelines for the management of severe traumatic brain injury[4-7] (although there have been calls for a randomized, controlled trial). Dissenting literature does exist. In two retrospective studies, there was no association[15] or a negative association[16] between monitoring-based treatment and outcome, and in an older, small, low-quality study of the usefulness of monitoring in guiding mannitol dosing, monitoring was not found to be useful.[17]

Since our study was conducted in Bolivia and Ecuador, the extent to which the findings can be generalized to other patient populations warrants discussion. Our data suggest that the care provided in the study hospitals adhered to the

Table 3. Processes of Care.*

Variable	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value†	Proportional Odds Ratio (95% CI)‡
Duration of ICP monitoring — days		—	—	—
Median	3.6			
Interquartile range	2.0–6.6			
Initial ICP ≥20 mm Hg — no./total no. (%)	55/147 (37)	—	—	—
ICP ≥20 mm Hg — % of readings		—	—	—
Median	7			
Interquartile range	1–31			
CPP ≤60 mm Hg — % of readings		—	—	—
Median	6			
Interquartile range	2–21			
Protocol-specified comparisons				
Length of stay in ICU — days			0.25	0.81 (0.55–1.18)
Median	12	9		
Interquartile range	6–17	6–16		
Length of stay in ICU with brain-specific treatment — days§			0.002	1.87 (1.28–2.75)
Median	3.4	4.8		
Interquartile range	1.1–7.0	2.3–7.4		
Respiratory complications — no. (%)	93 (59)	108 (65)	0.36	1.00 (0.63–1.59)
Sepsis — no. (%)	16 (10)	12 (7)	0.43	0.61 (0.27–1.41)
Decubitus ulcers — no. (%)	19 (12)	8 (5)	0.03	0.35 (0.15–0.85)
Non-neurologic complications — no. (%)	134 (85)	147 (88)	0.52	1.20 (0.62–2.34)

Table 3. (Continued.)

Variable	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value†	Proportional Odds Ratio (95% CI)‡
Post hoc comparisons¶				
Integrated brain-specific treatment intensity			<0.001	2.36 (1.60–3.47)
Median	69	125		
Interquartile range	13–181	45–233		
Individual treatments — no./total no. (%)				
Mannitol	80/157 (51)	94/166 (57)	0.25	1.32 (0.82–2.13)
Hypertonic saline	90/156 (58)	119/166 (72)	0.008	1.95 (1.19–3.22)
Furosemide	6 (4)	13 (8)	0.11	2.53 (0.82–7.81)
Hyperventilation	93 (60)	122 (73)	0.003	2.16 (1.29–3.61)
Cerebrospinal fluid drainage	1 (1)	3 (2)	0.37	2.84 (0.29–27.78)
Barbiturates	38 (24)	22 (13)	0.02	0.46 (0.25–0.83)
Neurosurgical procedures — no./total no. (%)				
Craniotomy for mass lesion	63/157 (40)	74/166 (45)	0.50	1.19 (0.76–1.86)
Craniectomy	44/157 (28)	49/166 (30)	0.81	1.04 (0.63–1.69)
Alone	9 (6)	9 (5)	1.00	0.93 (0.35–2.42)
With other neurosurgical procedure	35 (22)	40 (24)	0.79	1.07 (0.63–1.80)

* Additional variables measured as part of the processes of care are listed in Table S9A in the Supplementary Appendix for all patients who underwent randomization. Processes of care for brain-specific treatment for survivors only are listed in Table S7B in the Supplementary Appendix. CPP denotes cerebral perfusion pressure, ICP intracranial pressure, and ICU intensive care unit.

† P values for comparisons in which the median and interquartile range are provided were calculated with the use of a blocked Wilcoxon test[11]; all other P values were calculated with the use of Fisher's exact test.

‡ For proportional odds ratios, a value greater than 1 indicates a more favorable assessment for the pressure-monitoring group.

§ The length of stay in the ICU with brain-specific treatment was defined as the time up to last use of a treatment for intracranial hypertension other than ventilation, sedation, or analgesia.

¶ The treatment intensity for post hoc comparisons was defined as the number of different treatments for intracranial hypertension (other than ventilation, sedation, or analgesia) per hour, summed over the duration of brain-specific treatment, and counting high-dose mannitol, hypertonic saline, or hyperventilation as two treatments. See Table S9A in the Supplementary Appendix for details.

fundamentals of ICU care and was consistent with the study design. Prehospital resuscitation is less developed in Bolivia and Ecuador than in higher-income countries, and the more severely injured patients in those two countries may not survive long enough to reach the hospital. Thus, the study population may have had less severe brain injury than comparable ICU populations in higher-income countries. On the other hand, less advanced prehospital resuscitation may result in secondary insults (e.g., hypoxemia and hypotension), which would serve to increase the severity of the injury. In our study, the initial and subsequent readings of intracranial pressure, findings on CT, and pupillary responses were all consistent with very severe injury. The early outcome curves in our study appear to be consistent with what would be expected for young adults with severe brain injury whose care was being well managed in ICUs in wealthier countries. The results we report on early mortality were also similar to those reported in higher-income countries.[14] Survival at 6 months is confounded by high mortality (35% of the deaths) after the first 14 days, which is probably related to the limited resources available after discharge from the ICU. None of the study participants received rehabilitation or extensive medical care after hospital discharge. The elderly population with traumatic brain injury, which is prominent in high-income countries, was not represented in this study.

Between-group differences in the individual treatments delivered (with greater use of hypertonic saline, mannitol, and hyperventilation in the imaging–clinical examination group than in the

Table 4. Catheter-Related or Serious Adverse Events.*

Adverse Event	Pressure-Monitoring Group (N=157)	Imaging–Clinical Examination Group (N=167)	P Value†
	number (percent)		
Events related to ICP catheter‡	10 (6)	—	—
Infection	0	—	—
Catheter malfunction	4 (3)	—	—
Unplanned catheter removal	4 (3)	—	—
Hemorrhage	2 (1)	—	—
Any serious adverse event	70 (45)	76 (46)	0.91
Infections	13 (8)	10 (6)	0.52
Nervous system events, excluding infections	19 (12)	29 (17)	0.21
Respiratory system events, excluding infections	9 (6)	8 (5)	0.81
Cardiovascular system events	17 (11)	13 (8)	0.44
Death from an unspecified cause	12 (8)	12 (7)	1.00

* Additional adverse events are listed in Tables S10A and S10B in the Supplementary Appendix.
† Statistical significance was calculated with the use of Fisher's exact test.
‡ None of the catheter-related adverse events met the criteria for a serious adverse event.

pressure-monitoring group) reflect differences in approaches to treatment: scheduled treatment in the imaging–clinical examination protocol and treatment as indicated in the pressure-monitoring protocol. The quantitative measurement of intracranial pressure and the consequent fixed treatment threshold probably explains the more frequent administration of high-dose barbiturates and high-dose hypertonic saline in the pressure-monitoring group.

There was a need to standardize the type of monitoring used. Intraparenchymal monitoring was chosen for its accuracy,[7] ease of insertion, safety profile,[18] and low maintenance requirements. The alternative — a transduced ventricular catheter, which is accepted worldwide and was available but rarely used at the study sites before the start of the study — was not believed to be as compatible with our study setting, even though it offers the inherently useful therapeutic option of draining cerebrospinal fluid. Cerebrospinal-fluid drainage was a treatment option that would have required separate ventriculostomy placement — an approach to monitoring that is similar to that specified in the protocol for the ongoing Brain Tissue Oxygen Monitoring in Traumatic Brain Injury (BOOST 2) trial (ClinicalTrials.gov number, NCT00974259). Drainage of cerebrospinal fluid is consistent with guidelines-based management.[7] Although it is effective as a means of lowering elevated intracranial pressure temporarily,[19] drainage has not been shown to improve the outcome of severe traumatic brain injury.[20]

At issue here is not the question of whether intracranial pressure is important — both groups were treated for intracranial hypertension. We investigated whether the guidelines-based[7] protocol used in this study significantly improved the outcome. Our results do not support the superiority of treatment based on intracranial-pressure monitoring[7] over treatment guided by neurologic testing and serial CT imaging in improving short-term or long-term recovery in the general population of patients with severe traumatic brain injury. This finding does not argue against the use of intracranial–pressure monitoring. Only the monitoring-based interventional algorithm was tested here. It is possible that the imaging–clinical examination protocol provided superior control of intracranial pressure.[17] Alternatively, the lack of efficacy may be attributable to other factors, such as the use of a universal threshold for intracranial pressure or the efficacies and toxic effects of the therapeutic agents used, individually or in combination. Additional reasons for the lack of efficacy may include the interpretation of the data on intracranial pressure (a focus on instantaneous values rather than

trends or on intracranial pressure rather than cerebral compliance), the lack of identification of subtypes of traumatic brain injury requiring different approaches to management (subtype identification may evolve over the course of treatment), the universal primacy of manipulation of intracranial pressure as opposed to consideration of other physiological interventions (e.g., management of cerebral perfusion pressure), or even the consideration of intracranial pressure as a treatment variable rather than merely an indication of disease severity.

The value of knowing the precise intracranial pressure is not being challenged here, nor is the value of aggressively treating severe traumatic brain injury being questioned. Rather our data suggest that a reassessment of the role of manipulating monitored intracranial pressure as part of multimodality monitoring and targeted treatment of severe traumatic brain injury is in order.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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EDITORIALS

Intracranial pressure monitoring in severe traumatic brain injury

Should not be abandoned on the basis of recent evidence

Peter J Hutchinson *reader in neurosurgery*[1], Angelos G Kolias *National Institute for Health Research academic clinical fellow in neurosurgery*[1], Marek Czosnyka *reader in brain physics*[1], Peter J Kirkpatrick *consultant neurosurgeon*[1], John D Pickard *professor of neurosurgery*[1], David K Menon *professor of anaesthesia*[2]

[1]Division of Neurosurgery, Addenbrooke's Hospital and University of Cambridge, Cambridge CB2 0QQ, UK; [2]Division of Anaesthesia, Addenbrooke's Hospital and University of Cambridge, Cambridge, UK

In a trial recently published in the *New England Journal of Medicine*, Chesnut and colleagues attempted to provide class I evidence on the impact of intracranial pressure (ICP) monitoring on functional and neuropsychological outcomes after traumatic brain injury (TBI).[1] The authors concluded that there was no difference in the primary outcome—a composite of 21 equally weighted components—between the group of patients who had ICP monitoring and the group that did not. This is a landmark study; undertaking such a trial has long been considered impossible because most experts considered ICP monitoring the primary basis for managing patients with severe TBI.[2] However, the findings require some scrutiny before we can consider a fundamental change in our approach to managing these patients.

Since it was introduced into clinical practice more than 50 years ago, ICP monitoring has gradually become the standard of care in most centres that treat patients with severe TBI in the United Kingdom, North America, and most developed countries.[2] The physiological basis of ICP monitoring in TBI is twofold. Firstly, increasing ICP indicates escalating mass effect (from haematomas, contusions, or diffuse brain swelling). If escalating mass effect is left untreated, brain herniation and death will follow. Secondly, ICP has a direct impact on cerebral perfusion pressure (the mean arterial blood pressure minus ICP). It is important to maintain cerebral perfusion pressure to avoid brain ischaemia—one of the major factors that contribute to unfavourable clinical outcome after TBI.[2] ICP monitoring is used to guide the use of treatments for severe TBI, such as hyperventilation, osmotherapy, hypothermia, barbiturate coma, and decompressive craniectomy.

Numerous large cohort studies have shown that raised ICP (around 20-25 mm Hg) is independently associated with a higher risk of death after TBI.[3 4 5] However, a study published in 2012, a secondary analysis of data on 365 patients with severe TBI from a randomised trial, found no independent association between average ICP and neuropsychological functioning among survivors.[6] The only other study to question the usefulness of ICP monitoring was a retrospective cohort comparison study from the Netherlands, which showed that patients who received ICP monitoring were treated in the intensive care unit for longer than those whose ICP was not monitored, and outcomes were no better in the monitored group.[7] Nonetheless, because of abundant class II and III evidence, the Brain Trauma Foundation 2007 guidelines included a level II recommendation (moderate degree of clinical certainty) that ICP should be monitored in all salvageable patients with severe TBI.[2] In the UK, head injury guidelines from the National Institute for Health and Clinical Excellence state that treatment in a neuroscience centre would benefit all patients with severe TBI, irrespective of the need for neurosurgical intervention.[8] Moreover, a large cohort study has shown that management of severe TBI in neuroscience centres is associated with reduced mortality.[9]

With such widespread acceptance of ICP monitoring as the standard of care for patients with severe TBI, it would be difficult to recruit patients to a trial where one arm did not receive ICP monitoring. Chesnut and colleagues overcame this problem by identifying a group of intensivists in Bolivia and Ecuador who were unsure about its effectiveness and routinely managed their patients with severe TBI without ICP monitoring.[1]

The trial hypothesis was that a therapeutic protocol based on ICP monitoring would result in reduced mortality and improved neuropsychological and functional recovery compared with a therapeutic protocol based on imaging and clinical examination (control arm). Importantly, both arms received interventions aimed at lowering ICP, and it seems that significantly more patients in the control arm received osmotherapy and hyperventilation.[1] Furthermore, only 45% of participants were transported to the first hospital by ambulance. This should not

pjah2@cam.ac.uk

affect the internal validity of the trial because baseline characteristics were similar in the two arms, analysis was intention to treat, and the follow-up was 92% in both arms. However, external validity is certainly limited because the prehospital management of severe TBI is more advanced in the UK, North America, and most developed countries, where most patients with severe TBI are transported to hospital by ambulance.[10]

Chesnut and colleagues found no significant difference between groups in the primary outcome, which was a composite of 21 equally weighted components. Because 12 of the 21 items are neuropsychological tests, neuropsychological performance is highly influential in the composite endpoint.[1] This is of concern if considered in light of existing literature.[2 6] A more conventional outcome measure, the extended Glasgow outcome scale, showed a non-significant 5% difference in both mortality and favourable outcome (favouring the ICP arm).[1] Moreover, as the authors acknowledge, the risk of a type II error was high: with 324 cases, the study had only 40% power to detect a 10% increase in favourable outcome on the Glasgow outcome scale.

Although the study investigators should be congratulated for recruiting patients to reach the intended target, the results must be interpreted with extreme caution because of the high risk of a type II error. In our opinion, a move away from ICP monitoring in developed countries would be detrimental to the outcomes of patients with severe TBI. We also believe that a "normal" ICP should not be considered only in light of a particular cut-off value, because waveform analysis of the ICP is also important. Ongoing research has shown that ICP waveform analysis can provide information on the state of cerebrovascular reactivity (PRx index) and can be used to estimate optimal cerebral perfusion pressure levels for individual patients.[11 12] Finally, with increasing recognition of the heterogeneity of TBI, further integration of multimodality signals (ICP, brain microdialysis, brain tissue oxygenation, electrocorticography) could enable clinicians to deliver individualised treatments to patients with severe TBI.

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CORRESPONDENCE

Intracranial-Pressure Monitoring in Traumatic Brain Injury

TO THE EDITOR: In response to the article by Chesnut et al. (Dec. 27 issue)[1] reporting results of the trial on intracranial-pressure monitoring, we want to mention that environment must be taken into consideration to understand the role of intracranial-pressure monitoring on outcome. Approximately 80% of severe traumatic brain injuries occur in austere environments,[2] defined as regions lacking in prehospital and advanced care in an intensive care unit (ICU). Care within organized trauma systems has been shown to reduce mortality associated with severe traumatic brain injury.[3-5] Studies of traumatic brain injury in austere environments have shown rates of death that are 2 to 3 times as high as those in environments where advanced care is available.[6]

As the authors mention, several patients in this study arrived after 1 hour without appropriate prehospital care. In this real scenario, ICU monitoring has very little chance of making a difference by itself.

We are currently engaged in a study sponsored by the National Institutes of Health (Capacity Building for Decompressive Craniotomy in Colombia) to identify whether early surgical decompression may have an effect on outcome in such environments. The rationale for this approach is to prepare the cranial compartment for the brain response to the injury in cases in which ICU monitoring is not feasible and all we can rely on is the clinical evaluation.

Andrés M. Rubiano, M.D.
Neiva University Hospital
Neiva, Colombia
rubianoam@upmc.edu

Juan C. Puyana, M.D.
University of Pittsburgh Medical Center
Pittsburgh, PA

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THIS WEEK'S LETTERS

1748 **Intracranial-Pressure Monitoring in Traumatic Brain Injury**
1752 **Smoking-Related Mortality in the United States**
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1756 **Hepatocellular Carcinoma after the Fontan Procedure**

TO THE EDITOR: Chesnut et al. compare outcomes of intracranial-pressure monitoring with a strategy of imaging and clinical examination in patients with traumatic brain injury. Although the authors generally use a reasonable set of inclusion criteria, their indications for the placement of intracranial-pressure monitoring unfortunately differ from the recommendations in widely used national guidelines, which advise the use of computed tomography of the head, patient age, systolic blood pressure, and specific neurologic-

examination findings in addition to the score on the Glasgow Coma Scale (GCS) to determine the need for intracranial-pressure monitoring.[1] In addition, the study population included adolescents, a subgroup known to have better outcomes with traumatic brain injury than do adults,[2] although a subset analysis according to age was not presented. Furthermore, the investigators included data for patients who had a decrease in the GCS score up to 48 hours after injury. Such patients, who are known to have outcomes that differ from those of patients who initially present with poor GCS scores, may have potential confounding from nonbrain injuries that cause a delayed clinical decline.[3]

Finally, the use of a more widely used outcome metric, such as the modified Rankin scale,[4] instead of or in parallel with the 21-metric composite outcome used in this trial may have placed results in a broader clinical and functionally relevant context.

Debraj Mukherjee, M.D., M.P.H.
J. Manuel Sarmiento, B.A.
Chirag G. Patil, M.D.
Cedars–Sinai Medical Center
Los Angeles, CA
debraj.mukherjee@cshs.org

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Chesnut et al. report no significant difference in mortality between patients with severe traumatic brain injury who were treated with the use of a protocol of intracranial-pressure monitoring and those treated with the use of a protocol of imaging and clinical examination. We agree that intracranial pressure is a critical factor and that clinical indicators are one way to gauge intracranial pressure. However, estimating rather than measuring intracranial pressure led to more intensive treatment and a longer ICU stay, incurring greater cost. Also, important differences between this Latin American study and other studies conducted in the United States that have shown decreased mortality in the pressure-monitoring group[1,2] include differences in the monitoring protocol used, ventricular intracranial pressure monitoring and drainage of cerebrospinal fluid rather than parenchymal monitoring, and rare use of barbiturates in the U.S. studies. The findings of Chesnut et al. mandate the development of treatment algorithms that address the true complexity of traumatic brain injury. Although current guidelines[3] evaluate individual management components, there is currently no published management algorithm. In work with Chesnut and other colleagues, we have developed an algorithm (the algorithm flow chart is available with the full text of this letter at NEJM.org) that could provide a foundation for future clinical research and that can answer questions raised by the Latin American study.

Jamshid Ghajar, M.D., Ph.D.
Brain Trauma Foundation
New York, NY
ghajar@braintrauma.org
Nancy Carney, Ph.D.
Oregon Health and Science University
Portland, OR

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The study by Chesnut et al. showed that although the pressure-monitoring group had a slightly better outcome than the imaging–clinical examination group (44% and 39% with favorable outcome, and 39% and 44% deaths, respectively), this difference was not significant. The authors designed a well-constructed study that was based on genuine clinical equipoise. However, the findings must be interpreted with caution. Any form of monitoring will improve outcome only if the clinician correctly interprets the information gained and initiates appropriate medical or surgical intervention. Unfortunately, intracranial pressure is essentially a gross measure of end-organ injury, and although it provides important

prognostic information, many traditional therapies that are used to lower intracranial pressure have failed to provide clinical benefit.[1-3] What is really needed is a more dynamic measure of the developing pathophysiological response to injury and new therapeutic interventions that can interrupt or modify the numerous biologic and metabolic cascades that are initiated at the time of the primary brain injury and in many cases amplified by secondary insults.[4] This must be the focus of future research.

Pasquale De Bonis, M.D.
Carmelo Anile, M.D.
Catholic University School of Medicine
Rome, Italy
debonisvox@gmail.com

Stephen Honeybul, F.R.C.S. (S.N.), F.R.A.C.S.
Royal Perth Hospital
Perth, WA, Australia

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Chesnut et al. found that among patients with a GCS score of less than 8, outcomes in those treated to maintain an intracranial pressure below 20 mm Hg were the same as in those treated on the basis of imaging and clinical examination. This is not surprising in a heterogeneous patient cohort with various pathoanatomic injury types and propensities for brain swelling, all of whom had very careful clinical observation and frequent imaging, and whose protocol-driven interventions were similar, varying mostly according to the timing of administration.

The incremental value of intracranial-pressure monitoring probably would benefit only a small subset of patients in whom an increase in pressure results in otherwise-undetected dangerous tissue shifts that are not responsive to the standardized management provided in this study. Stratifying patients according to a multidimensional classification system of traumatic brain injury that accounts for these factors, rather than according to the GCS score, is likely to be necessary to link specific patterns of brain injury with intracranial-pressure monitoring and other types of evaluation that are most likely to be of benefit.[1-3]

Kristopher T. Kahle, M.D., Ph.D.
Ann-Christine Duhaime, M.D.
Massachusetts General Hospital
Boston, MA
aduhaime@partners.org

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: We agree with Chesnut et al. that intracranial pressure should be interpreted as part of a multimodal monitoring approach. Indeed, in patients admitted for traumatic brain injury, it has been established that extracellular metabolic markers are independently associated with outcome.[1] This multimodal monitoring approach consists of metabolic monitoring (brain-tissue oxygen level and microdialysis) or blood-flow evaluation (transcranial Doppler studies). Therapy that is based on brain-tissue oxygen level has been shown to be associated with better outcomes than therapy based on intracranial pressure.[2] In the presence of decreased cerebral arterial oxygen content, whether due to hypoxemia or moderate hemodilution, increasing the cerebral blood flow allows maintenance of cerebral oxygen delivery.[3] Near-infrared spectroscopy is a relatively new technique that is available for noninvasive monitoring of cerebral oxygenation.[4] Near-infrared spectroscopy can be started early and may help identify patients at risk for low cerebral arterial content. We believe that near-infrared spectroscopy should be implemented in future studies to help monitor cerebral oxygenation as an end point.

Clément Dubost, M.D.
Pierre Pasquier, M.D.
Stéphane Mérat, M.D.
Begin Military Hospital
Saint-Mandé, France
clement.dubost@hotmail.fr

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Regarding the comments by Mukherjee et al. on our study design: we used monitoring indications that followed the guidelines of the Brain Trauma Foundation.[1] Post hoc analysis of outcomes according to age showed no differences between groups (see Table S8 in the Supplementary Appendix, available with the full text of our article at NEJM.org). The inclusion of patients who had deteriorating status within 48 hours after injury intentionally paralleled the criteria of the Traumatic Coma Data Bank, and this subgroup was symmetrically distributed ($P>0.05$) (Table S6 in the Supplementary Appendix). Scores on the individual, widely used outcome metrics (the Extended Glasgow Outcome Scale and the Disability Rating Scale) obtained from the composite score revealed no significant differences between the treatment groups (Tables S7A and S7B in the Supplementary Appendix).

We agree with the points of Ghajar and Carney, De Bonis et al., Kahle and Duhaime, and Dubost et al. that it is not monitoring per se but how the information derived from monitoring is used that is important. We must refocus on underlying pathophysiological features. Intracranial pressure is not the issue; there are compartmental shifts, abnormal intracranial compliance, and pressure-related perfusion deficits, which intracranial-pressure measures only partially reflect. Probing abnormal physiology by means of intracranial-pressure measurement, combined selectively with other monitoring strategies, should facilitate injury subcategorization, thus allowing treatment individualization, and therapeutic advancements.

Rubiano and Puyana correctly note that our arrival cohort probably differs from patients in centers with sophisticated prehospital care. We believe that higher prehospital mortality counterbalanced an increase in early secondary brain insults, but we were unable to quantify this factor. Data from imaging and clinical examination on arrival show a severely injured but salvageable young cohort. Examining mortality at 14 days (with accommodation for the high [30%] mortality after discharge that is related to unsophisticated resources outside the hospital), we find that outcomes are similar to those of high-income countries. ICU data support excellent, attentive medical care, confirming our subjective observations. We believe that the ICU-period data are sufficiently applicable to high-income countries.

Ethical queries that were raised in commenting on our article at NEJM.org also warrant a response. We addressed scientific support for treatment driven by the results of intracranial-pressure monitoring,[1] not its clinical popularity.[2-5] Investigators and ethics committees at every site preapproved this study. Explicitly trained study physicians obtained written informed consent from the participants or their representatives that used language approved by the institutional review boards. Investigators received thorough, repeated training in intracranial-pressure monitoring and the treatment protocol; protocol violations were infrequent (see the Supplementary Appendix). An analysis of results over time revealed no learning curve for monitoring. In the absence of published algorithms, protocol interventions in the imaging–clinical examination group mirrored the current practices of the investigators; no substandard treatments were involved. The demonstrated efficacy of the imaging–clinical examination protocol allays questions about the propriety of treatments.

Randall M. Chesnut, M.D.
University of Washington
Seattle, WA
chesnutr@uw.edu

Gustavo Petroni, M.D.
Carlos Rondina, M.D.
Hospital de Emergencias Dr. Clemente Alvarez
Santa Fe, Argentina

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Smoking-Related Mortality in the United States

TO THE EDITOR: The article by Thun et al. (Jan. 13 issue)[1] concluded that the risk of death from cigarette smoking continues to increase. Some issues, however, remain unclear. First, the effect of other risk factors that act in synergy with cigarette smoking has not been adequately weighted. Air pollution, for instance, may have finally contributed to bias in smoking-related outcomes, especially in relation to chronic obstructive pulmonary disease (COPD) and all-cause mortality.[2,3] It is also noteworthy that the makeup of cigarettes and the composition of cigarette smoke have changed remarkably in the past 50 years, such that a direct comparison of clinical outcomes may be misleading. In the United States, in particular, the sales-weighted average yields of "tar" (the residue produced by the burning of the cigarette) and nicotine have both declined from a high of 38 mg of tar and 2.7 mg of nicotine per cigarette in the 1950s to 12 mg and 0.95 mg, respectively, in the 1990s. The amounts and types of other harmful constituents of smoke have also changed since the 1950s.[4]

Giuseppe Lippi, M.D.

Academic Hospital of Parma
Parma, Italy
ulippi@tin.it

Camilla Mattiuzzi, M.D.

General Hospital of Trento
Trento, Italy

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In his editorial on the article by Thun et al., Schroeder[1] notes that as smoking becomes less popular, those who continue to smoke will be increasingly marginalized. This is particularly true for patients with psychiatric disorders, who already undergo the stigma and marginalization associated with mental illness; these patients also have the highest prevalence of smoking among all patient subgroups. Approximately two thirds of patients with schizophrenia and half of patients with bipolar disorder smoke,[2] although, as with smokers who do not have a psychiatric disorder, most of them want to quit smoking.[3] Unfortunately, misperceptions about mental illness and tobacco use often prevent clinicians from offering evidence-based treatment for tobacco dependence to patients with psychiatric disorders,[3] despite the fact that life expectancy for these patients is approximately 10 years lower than that for the general population because of premature deaths from medical illnesses that are largely attributable to tobacco use.[4] The isolation, coexisting conditions, and lower life expectancy of persons with mental illness will not be lessened unless smoking cessation is made a top priority for this vulnerable population.

Joseph M. Cerimele, M.D.
Abigail C. Halperin, M.D., M.P.H.

University of Washington School of Medicine
Seattle, WA
cerimele@uw.edu

No potential conflict of interest relevant to this letter was reported.

ALGORITHM FOR THE MANAGEMENT OF INTRACRANIAL HYPERTENSION AND ISCHEMIA IN PATIENTS WITH SEVERE TBI

Place ICP monitor*

ICP > 20

Tier 1

-CSF drainage (continuous or intermittent)
-Low dose mannitol 0.25-1.0/kg bolus

Tier 2

-Therapeutic mild hypothermia T 35-37
-Hypertonic saline by bolus or continuous infusion
-High dose mannitol > 1.0g/kg bolus
-Moderate hyperventilation to PaCO2 30-35 (not recommended in the presence of ischemia)

Tier 3

-High Dose barbiturates
-Neuromuscular blockade
-Decompressive craniectomy in the absence of surgical mass lesions
-Therapeutic Deep hypothermia T 32-34

Ischemia †

Tier 1

-Ventilation manipulation to maintain Pa02 > 90
-CPP manipulation to 50-70 with vasoactive medication

Tier 2

-Therapeutic mild hypothermia T 35-37

Algorithm Options

- Use ICP>20 and/or Ischemia pathways as needed.
- Treatments in a tier box can be used in any order.
- It is not necessary to use all of the modalities in a given tier prior to moving to the next tier.
- There is no rank ordering within a tier.
- When considered advantageous, tiers can be skipped when advancing treatment (e.g. early decompresssive craniectomy.)

Place ICP monitor* for GCS<9 and abnormal CT. Normal CT plus 2 out of 3 of the following parameters is an indicator for ICP Monitoring: GCS motor 1 or 2, Age >40, or SBP < 90 mm Hg at any time. Follow the recommendations in the Guidelines for the Management of Severe TBI-www.braintrauma.org.

Ischemia† in this algorithm is defined in the manuscript text of the Algorithm for Management of Severe TBI-A Systematic Approach for Achieving Consensus.

This algorithm is not intended to be a substitute in any way for care and treatment by a qualified healthcare professional.