Marked reduction in mortality in patients with severe traumatic brain injury

Clinical article

LINDA M. GERBER, PH.D.,¹ YA-LIN CHIU, M.S.,¹ NANCY CARNEY, PH.D.,²
ROGER HÄRTL, M.D.,³ AND JAMSHID GHAJAR, M.D., PH.D.^{4,5}

Departments of ¹Public Health and ³Neurological Surgery, Weill Cornell Medical College; and ⁴Brain Trauma Foundation, New York, New York; ⁵Department of Surgery, Jamaica Hospital Medical Center, Queens, New York; and ²Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon

Object. In spite of evidence that use of the Brain Trauma Foundation *Guidelines for the Management of Severe Traumatic Brain Injury* (Guidelines) would dramatically reduce morbidity and mortality, adherence to these Guidelines remains variable across trauma centers. The authors analyzed 2-week mortality due to severe traumatic brain injury (TBI) from 2001 through 2009 in New York State and examined the trends in adherence to the Guidelines.

Methods. The authors calculated trends in adherence to the Guidelines and age-adjusted 2-week mortality rates between January 1, 2001, and December 31, 2009. Univariate and multivariate logistic regression analyses were performed to evaluate the effect of time period on case-fatality. Intracranial pressure (ICP) monitor insertion was modeled in a 2-level hierarchical model using generalized linear mixed effects to allow for clustering by different centers.

Results. From 2001 to 2009, the case-fatality rate decreased from 22% to 13% ($p < 0.0001$), a change that remained significant after adjusting for factors that independently predict mortality (adjusted OR 0.52, 95% CI 0.39–0.70; $p < 0.0001$). Guidelines adherence increased, with the percentage of patients with ICP monitoring increasing from 56% to 75% ($p < 0.0001$). Adherence to cerebral perfusion pressure treatment thresholds increased from 15% to 48% ($p < 0.0001$). The proportion of patients having an ICP elevation greater than 25 mm Hg dropped from 42% to 29% ($p = 0.0001$).

Conclusions. There was a significant reduction in TBI mortality between 2001 and 2009 in New York State. Increase in Guidelines adherence occurred at the same time as the pronounced decrease in 2-week mortality and decreased rate of intracranial hypertension, suggesting a causal relationship between Guidelines adherence and improved outcomes. Our findings warrant future investigation to identify methods for increasing and sustaining adherence to evidence-based Guidelines recommendations.

(<http://thejns.org/doi/abs/10.3171/2013.8.JNS13276>)

KEY WORDS • intracranial pressure monitoring • guidelines • mortality • traumatic brain injury

TRAUMATIC brain injury (TBI) remains a lethal injury with mortality rates as high as 50%.^{5,8,12,18} In the United States, approximately 1.5 million people sustain TBI annually, resulting in over 50,000 deaths and 500,000 individuals with permanent neurological sequelae.^{24,26} Approximately 85% of mortality from TBI occurs within the first 2 weeks, reflecting the early effect of systemic hypotension and intracranial hypertension (ICH).²²

Prospective databases have played an important role in understanding the natural history, definition, assess-

ment, prognosis, and outcome of TBI.^{6,9,17,19} The knowledge of TBI gained from these registries resulted in a number of large pharmaceutical trials that attempted to translate promising results from the laboratory and pre-clinical trials into clinical practice. However, all of these pharmaceutical trials for TBI failed to demonstrate efficacy in reducing mortality.²¹

The failed pharmaceutical trials and widely heterogeneous TBI care across North America¹³ led a group of neurosurgeons and TBI experts to critically review and grade the existing evidence on the treatment of TBI using the process of evidence-based medicine. This work resulted in the 1996 publication of the first edition of the *Guidelines for the Management of Severe Head Injury*¹⁴ by the Brain Trauma Foundation in collaboration with

Abbreviations used in this paper: CI = confidence interval; CPP = cerebral perfusion pressure; GCS = Glasgow Coma Scale; ICH = intracranial hypertension; ICP = intracranial pressure; OR = odds ratio; SBP = systolic blood pressure; TBI = traumatic brain injury.

the American Association of Neurological Surgeons. The most recent iteration of these Guidelines was published in 2007 (referred to in this paper as the “Guidelines”).¹

In 2001 the New York State Department of Health approved a demonstration project to provide increased Medicaid funding to trauma centers that participated in a program to increase Guidelines adherence. The Brain Trauma Foundation designed and implemented a program to collect prospective data on patients with severe TBI. The purpose of the project was to disseminate and promote the use of the Guidelines in Level I and II trauma centers in New York and to measure the relationship between adherence to the Guidelines and outcomes. A focus was to increase adherence to the Guidelines recommendations for when to place an intracranial pressure (ICP) monitor and for ICP and cerebral perfusion pressure (CPP) management, as well as adherence to other recommendations that had Class 1 or Class 2 supporting evidence. Trauma centers that signed a participation agreement with the Brain Trauma Foundation committed to abstract data from medical records for patients who met predetermined eligibility criteria and to enter data into the Brain Trauma Foundation database, TBI-trac. They also agreed to convene a multidisciplinary team on a quarterly basis to review reports provided by the foundation, and act accordingly to implement improvements in patient practice. In exchange, the Brain Trauma Foundation agreed to provide quarterly reports, including “compliance scoring” relative to the recommendations contained in the Guidelines. The foundation also agreed to provide training and full access to the continuing education portion of its website. Upon confirmation from the foundation that a hospital signed the contract for a given year, the New York State Department of Health increased the hospital’s Medicaid payment rate for that year.

Recent publications from the TBI-trac database demonstrate that 1) mortality rates are higher in patients with severe TBI treated without ICP monitors than in those with monitoring;¹⁰ 2) response to ICP treatment significantly predicts reduction in mortality;¹¹ 3) adherence to the nutrition recommendations in the Guidelines significantly improves outcomes;¹⁶ and 4) direct transport of severe TBI patients to a Level I or Level II trauma center reduces mortality.¹⁵

The primary goals of the current study were to analyze 2-week mortality due to severe TBI between 2001 and 2009 in New York State and to examine the trends in adherence to the Guidelines.

Methods

The TBI-Trac Database

As stated, as part of a quality improvement initiative, the Brain Trauma Foundation designed and implemented a program, funded by the New York State Department of Health. The program uses an online Internet database, TBI-trac, to collect data on patients with severe TBI to be used by trauma centers to track adherence to the Guidelines and as a prospective database to test hypotheses that could improve the Guidelines. This database contains clin-

ical information from prehospital sources, the emergency department, the first 10 days in the intensive care unit, and 2-week mortality data from 22 of the 46 designated trauma centers in New York State. Of the 22 participating sites, 20 are Level I trauma centers and 2 are Level II.

Hospitals volunteered to participate. Data from participating trauma centers were entered by trained trauma nurse coordinators. This report is based on patients treated in these trauma centers between January 1, 2001, and December 31, 2009. The research protocol was approved or deemed exempt from review by the institutional review boards of each of the participating centers. In compliance with Health Insurance Portability and Accountability Act regulations, the database refrains from the use of patient identifiers, thereby ensuring confidentiality for the data sets at each institution.

Study Population

The TBI-trac database includes data from cases of severe TBI involving patients of any age who have isolated or multitrauma TBI and meet the following criteria: arrival at the participating trauma center within 24 hours of injury and a Glasgow Coma Scale score (GCS) less than 9, with a GCS motor score less than 6 for at least 6 hours after injury and after resuscitation efforts, including airway management, ventilatory support, and circulatory support. The mechanism of injury had to be consistent with trauma. Patients with severe TBI who died in the emergency department or were admitted with the diagnosis of brain death were excluded. Data pertaining to patients who were not paralyzed and had a GCS score of 3 or 4 with fixed and dilated pupils on Day 1 or 2 following trauma were recorded but excluded from analysis, since these patients were unlikely to benefit from ICP-lowering therapies.

Adherence Measures

We used the recommendations of the Guidelines¹ to investigate trends in adherence to the Guidelines. Adherence was defined as follows:

Intracranial Pressure Monitoring. An abnormal CT scan or at least 2 of 3 of the following criteria: age > 40, hypotension, or GCS motor score of 1, 2, or 3.

Intracranial Hypertension Treatment Threshold. An ICP > 25 mm Hg for at least 1 hour in patients who had an ICP monitor inserted during Day 1 or 2 following admission.

Treatments for ICH on Days 1 and 2. The administration of at least 1 of the following ICP treatment regimens in the first 2 days following admission: mannitol, hypertonic saline, barbiturates, drainage of cerebrospinal fluid, or decompressive craniectomy.

Cerebral Perfusion Pressure Treatment Thresholds. In patients with an ICP monitor: CPP ≥ 60 mm Hg every day if age ≥ 12 years; CPP ≥ 50 if age 6–11 years; CPP ≥ 40 if age ≤ 5 years. The guideline for age ≥ 12 years was changed to 50–70 mm Hg in midyear 2008.

Hypotension Threshold. Systolic blood pressure (SBP) < 90 mm Hg for ages ≥ 12 years; SBP < 80 mm Hg

Marked reduction in mortality in patients with severe TBI

for ages 6–11 years; and SBP < 75 mm Hg for ages 1–5 years on any day.

Steroid Medication. No administration of steroid medication on any day for severe TBI treatment.

Nutrition. Received the caloric intake of ≥ 25 kcal/kg/day on any day by Day 7.

Statistical Analysis

Descriptive statistics were calculated for patient characteristics, and bar charts were plotted for trends in mortality, treatment, and ICP. Time periods were categorized as 2001–2003, 2004–2006, and 2007–2009. The case-fatality rate for each time period was calculated as the total number of deaths divided by the total number of patients in the TBI-trac database multiplied by 100. The crude mortality rate for each year was calculated as the ratio of deaths for that year in the TBI-trac database to the New York State population in that same year per 100,000. Expected deaths were calculated by multiplying the age-specific crude mortality rates by the age-specific population of the United States on June 1, 2000 (standard population). The summation of the expected number of deaths across all age groups, divided by the total standard population, constitutes the age-adjusted mortality rate for each year. The crude mortality rates per time period were calculated as the ratio of the average number of deaths to the average of the New York State population across years per 100,000. The final age-adjusted mortality rates per time period were calculated as the ratio of the average number of expected deaths across years to the standard population. The chi-square test was used to compare case-fatality, prevalence, and adherence rates between time periods (pairwise comparisons). In addition, univariate and multivariate logistic regression analyses were performed to evaluate the effect of time period on case-fatality. Covariates included in the multivariate model were age, hypotension status on Day 1, pupillary status on Day 1, initial GCS score, and CT scan results.

Patient-level ICP monitor insertion (1 = yes, 0 = no) was modeled in a 2-level hierarchical model using generalized linear mixed effects to allow for clustering by different centers. (Patient-level refers to the unit of observation being at the patient level, as opposed to center level.) The fixed effects part of this mixed model had an intercept and slope to model the center-average (average across all centers) baseline effect (1st year ICP monitor insertion rate) and time trend, respectively. A random intercept was used to model heterogeneity of baseline ICP monitor insertion across centers and a random slope to model the heterogeneity of time trends across centers. Centers with less than 10 qualifying cases (cases that met the inclusion criteria for this study) recorded in the TBI-trac database over the study period were excluded from this analysis. In addition, fixed and random effects were introduced for the quadratic term (for year), but the corresponding random effect was dropped as it was not significant. The variances of random effects, the estimates of fixed effects, and p values were reported. The center-specific predicted probabilities as well as the center-average predicted probabilities for each year

were calculated and plotted. Odds ratios (OR) and 95% confidence intervals (CI) from the logistic regression models were reported. All p values are 2-sided with statistical significance evaluated at the 0.05 alpha level. Analyses were performed in SAS version 9.2 (SAS Institute, Inc.).

Results

Characteristics of the Study Sample

Most of the trauma centers (90.9%) were Level I centers. An average of 261 cases per year were entered into the database. The volume of patients per center between 2001 and 2009 ranged from 202 to 334.

Between January 1, 2001, and December 31, 2009, data for 2999 patients were entered into the database. After exclusion criteria were applied, 2347 cases were eligible for analysis. Mortality data were missing for 27 (1.2%) of these 2347 cases. Thus, 2320 cases were included for the analyses of mortality.

The demographic and clinical characteristics of the study population are presented in Table 1. The patients' mean age was 36.8 years (SD 20.6 years), and 76.3% were male. The admission GCS score was 3–5 in 50.7% of the

TABLE 1: Characteristics of the study population*

Characteristic	Total
no. of patients	2347
age in yrs	
mean $\pm$ SD	36.8 $\pm$ 20.6
<18	336 (14.3%)
≥ 18	2011 (85.7%)
male sex	1791 (76.3%)
initial GCS score	
3–5	1178 (50.7%)
6–8	1146 (49.3%)
hypotension present on Day 1	
yes	353 (15.3%)
no	1955 (84.7%)
CT findings	
normal	404 (18.1%)
abnormal	1827 (81.9%)
pupillary abnormalities	
yes	461 (20.0%)
no	1850 (80.0%)
barbiturate use on Day 1 or 2	
yes	60 (2.6%)
no	2270 (97.4%)
ICP monitoring on Day 1 or 2	1506 (64.2%)
type of ICP monitoring	
ventriculostomy only	1050 (69.7%)
parenchymal only	416 (27.6%)
other	14 (0.9%)
>1 monitoring type	26 (1.7%)

* Values represent numbers of patients (%) unless otherwise indicated.

cases and 6–8 in 49.3%; 84% of the total patient group qualified for ICP monitoring according to recommendations in the Guidelines.

Mortality Trends From 2001 Through 2009

Age-adjusted severe TBI mortality rates from 2001 through 2009 are displayed in Fig. 1 (left). Severe TBI mortality rates, for both unadjusted and adjusted mortality, declined by approximately 45% from 0.31 per 100,000 population in 2001–2003, to 0.17 per 100,000 population in 2007–2009. Of patients in the 22 trauma centers being treated for severe TBI, the case-fatality rate (Fig. 1 right) decreased from 22.4% to 13.3% over the decade (crude OR 0.53, 95% CI 0.40–0.72; $p < 0.0001$). Between 2007 and 2009, the rate was approximately half that of 2001–2003. This decline in mortality remained after adjusting for factors that independently predict mortality (adjusted OR 0.52, 95% CI 0.39–0.70; $p < 0.0001$).

Trends in Guidelines Adherence Between 2001 and 2009

The proportion of patients who had an ICP monitor increased between 2000 and 2009 (Fig. 2 left). Where 55.6% of patients had ICP monitoring between 2001 and 2003, this percentage increased to 72.3% between 2004 and 2006 and to 75.2% between 2007 and 2009 ($p < 0.0001$). Additionally, there was a significant association ($p = 0.0002$) between mortality and ICP compliance such that mortality in the noncompliance group was 25.8% compared with 18.6% in the ICP compliance group. Over the decade, the proportion of patients having an ICP elevation greater than 25 mm Hg on either the 1st or 2nd day in the hospital dropped from 41.5% to 29.0% ($p = 0.0001$, Fig. 2 right). Treatment for elevated ICP has been

consistently high throughout the decade (Fig. 2 right). Adherence to CPP treatment thresholds increased over the decade, from 14.6% in the early part of the decade to 48.2% by 2009 ($p < 0.0001$, Fig. 3A). Cerebral perfusion pressure management compliance was strongly related to decreases in ICH (Fig. 4). Adherence to the Guidelines recommendations for nutrition improved from 41.0% to 50.1% over the decade ($p = 0.005$, Fig. 3B). Adherence to the Guidelines recommendations for steroids was high throughout the decade (Fig. 3C). The in-hospital rate of hypotension remained low from 2001 to 2009 (2001–2003, 6.3%; 2004–2006, 6.5%; 2007–2009, 7.1%).

Variability of ICP Monitoring Between Centers From 2001 Through 2009

All centers had increased probability of ICP monitor insertion over the time period; however, the rate of increase tended to decrease over time with considerable heterogeneity in baseline and time trend across centers (Fig. 5). The fixed effect estimate of time (year: 0.39, $p = 0.0002$) depicting the center-average rate of increase of probability of ICP monitor insertion per year was significant, implying that the center-average insertion rate increased over the years. The fixed effect estimate for the quadratic term (year²: -0.03, $p = 0.01$) depicting the rate of increase of ICP insertion decreased over time. The baseline heterogeneity across centers (variance of random intercept) was 0.67 ($p = 0.02$ for testing different from 0) implying significant heterogeneity. The heterogeneity in time trend across centers (variance of random slope) was 0.04 ($p = 0.01$ for testing difference from 0) implying that the trend of ICP monitor insertion rates was significantly different across centers. In other words, some centers had better improvement than others. Year 2002 had 44%

Fig. 1. Graphs showing the change in crude and age-adjusted mortality rates (left) and case-fatality rates (right) over the study period. (For definitions of case-fatality and age-adjusted mortality rates, see *Methods*.) With respect to case-fatality, significant differences were found between the rates for 2001–2003 and 2007–2009 ($p < 0.0001$) and between the rates for 2004–2006 and 2007–2009 ($p < 0.001$).

Marked reduction in mortality in patients with severe TBI

Fig. 2. **Left:** Graph showing change in prevalence of ICP monitor insertion. Significant differences were found between the rate for 2001–2003 and the rate for 2004–2006 ($p < 0.0001$) and between the rate for 2001–2003 and the rate for 2007–2009 ($p < 0.0001$). **Right:** Graph showing the prevalence of ICP elevation and treatment for ICH. Significant differences were found comparing rates for ICP elevation between 2001–2003 and 2007–2009 ($p = 0.0001$) as well as between 2004–2006 and 2007–2009 ($p = 0.0004$). There were no significant differences in rates for treatment for ICH between time periods.

higher odds of ICP monitor insertion compared with Year 2001 (OR 1.44, 95% CI 1.35–1.54). Over the study period, Year 2009 had 4 times higher odds of ICP insertion compared with Year 2001 (OR 4.10, 95% CI 2.79–6.03).

Discussion

This prospective database analysis from New York

State demonstrates a remarkable decrease in age-adjusted mortality among patients with severe TBI from 2001 through 2009. This decline occurred within a quality improvement initiative undertaken by the Brain Trauma Foundation in New York. The main goal of the initiative was to increase adherence to the Guidelines for management of severe TBI, which did occur. Most notable was a marked increase in adherence to ICP monitoring recom-

Fig. 3. Graphs showing rates of adherence to Guidelines. **A:** Significant differences were found for adherence to the Guidelines with respect to CPP treatment thresholds between 2001–2003 and 2004–2006 ($p < 0.0001$), between 2001–2003 and 2007–2009 ($p < 0.0001$), and between 2004–2006 and 2007–2009 ($p < 0.0001$). **B:** Significant differences were found between 2001–2003 and 2007–2009 ($p = 0.005$) for adherence to the nutrition guideline. **C:** Significant differences were found between 2004–2006 and 2007–2009 ($p = 0.008$) for adherence to the guideline regarding the use of steroid medication.

Fig. 4. Graph showing the prevalence of ICH by CPP adherence. Significant differences were found for the time periods 2004–2006 ($p < 0.0001$) and 2007–2009 ($p < 0.0001$).

mentations and a striking increase in adherence to CPP management recommendations. Concurrently there was a significant reduction in the rate of ICH.

Previous studies reported lower mortality and morbidity rates when ICP monitoring was used in a protocol-based manner in neurosurgical intensive care units.² Evidence in the past has been derived from meta-analyses of small retrospective studies or from larger databases that were not risk-adjusted to address the independent effect

of ICP monitoring.²⁵ A recent study by Chesnut et al.,⁷ carried out in South America, found no 2-week mortality differences in an ICP-directed treatment protocol versus a CT/clinical signs-directed protocol. However, the study reported more ICU days and intensity of treatments in the CT/clinical indicator group, which would increase costs compared with the ICP-directed protocol. There was also a 2-fold increase in initial pupillary abnormalities in the South American study compared with this New York

Fig. 5. Graph showing that the rate of ICP insertion increased over time and the rate of increase tended to decrease over time (year²: -0.03 , $p = 0.009$). There was significant heterogeneity at baseline across centers (variance of random intercept = 0.73 , $p = 0.02$). The trend with respect to ICP monitor insertion rates differed significantly across centers (variance of random slope = 0.04 , $p = 0.01$).

Marked reduction in mortality in patients with severe TBI

State study, which could reduce protocol effectiveness. In addition, in New York State, ventricular ICP monitoring with drainage of cerebrospinal fluid was used in the majority of cases, and barbiturates were used rarely.

The current study demonstrates a significant association between ICP compliance and reduced mortality. Consistent with previous work from the Brain Trauma Foundation's TBI-trac database, patients of all ages treated with an ICP monitor in place had lower mortality rates at 2 weeks ($p = 0.02$) than those treated without an ICP monitor, after adjustment for parameters that independently affect mortality.¹⁰ This finding suggests that treatment of suspected ICH without definitive information may actually be a risk factor for mortality, providing further evidence that information from ICP monitoring improves the management of ICH in patients with severe TBI.²⁷

These results strongly suggest a key role of CPP management in the reduction of mortality over time. Many studies have also shown a strong relationship between CPP thresholds and better outcomes with lower mortality.^{3,4,20,23} When high ICP was detected, adherence to ICP treatment was consistently over 90% throughout this study. However, ICH was reduced (from 42% to 40% to 29%) when the CPP threshold rate improved (from 15% to 34% to 48%), indicating that *both* ICP control and CPP control contributed to the reduction in mortality. These findings call for further investigation of specific, targeted treatment to manage CPP within recommended parameters.

On the other hand, our findings show significant variation across centers with respect to adherence to the Guidelines recommendations for ICP monitoring and also a consistently low adherence (across time, for all centers) to the Guidelines recommendations for nutrition. This is especially concerning since previous work has shown the importance of early nutrition in these patients.¹⁶ While the center variation may be due to small sample sizes at the center level, both findings call for closer attention to questions such as 1) what drives adherence to the Guidelines at the center level and 2) what further improvements in outcome would be observed with closer adherence to evidence-based treatments, like nutrition, that occur in less acute circumstances. These questions, and a controlled study of CPP management, are important topics for future research.

Conclusions

There was a significant reduction in mortality over 9 years among patients with severe TBI in New York State trauma centers as part of the New York State–Brain Trauma Foundation quality improvement program. This reduction appears to be associated with an increase in adherence to the Guidelines recommendations for ICP monitoring and CPP management. Concurrent with increased ICP monitoring and CPP management, the rate of ICH decreased significantly over 9 years. During the same time period, there have not been significant changes in adherence to other Guidelines recommendations, suggesting that increased ICP monitoring and CPP management improved outcomes.

Two key questions for future research are 1) what

specific CPP management approaches are most effective in which subgroups of patients with TBI and 2) what is required to change medical practice so that evidence-based treatments are widely adopted and followed.

Acknowledgments

We acknowledge the administrative support for manuscript preparation and submission provided by Meredith Klein, Brain Trauma Foundation, and Amy Huddleston, M.P.A., Oregon Health & Science University.

Disclosure

The Brain Trauma Foundation funded the development of the database TBI-Trac. The trauma centers and the Brain Trauma Foundation were funded by New York State Department of Health, Division of Healthcare Financing and Acute and Primary Care reimbursement to implement the TBI-Trac database quality assurance program. The NewYork-Presbyterian Hospital TBI fund supported the data analysis.

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Dr. Härtl is a consultant for Brainlab, DePuy Synthes, Lanx, and Spine-Wave. Dr. Ghajar is president of the Brain Trauma Foundation.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ghajar, Gerber, Härtl. Acquisition of data: Ghajar, Gerber, Chiu. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ghajar. Statistical analysis: Ghajar, Gerber, Chiu. Administrative/technical/material support: Gerber. Study supervision: Ghajar, Gerber.

References

1. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Härtl R, et al: Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma* **24** (Suppl 1):S7–S13, 2007 (Erratum in *J Neurotrauma* **25**:276–278, 2008)
2. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Härtl R, et al: Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma* **24** (Suppl 1):S55–S58, 2007 (Erratum in *J Neurotrauma* **25**:276–278, 2008)
3. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Härtl R, et al: Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma* **24** (Suppl 1):S59–S64, 2007 (Erratum in *J Neurotrauma* **25**:276–278, 2008)
4. Budohoski KP, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, et al: The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. *Neurosurgery* **71**:652–661, 2012
5. Bulger EM, Nathens AB, Rivara FP, Moore M, MacKenzie EJ, Jurkovich GJ: Management of severe head injury: institutional variations in care and effect on outcome. *Crit Care Med* **30**:1870–1876, 2002
6. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF: Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)* **59**:121–125, 1993
7. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al: A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* **367**:2471–2481, 2012

8. Demetriades D, Kuncir E, Murray J, Velmahos GC, Rhee P, Chan L: Mortality prediction of head Abbreviated Injury Score and Glasgow Coma Scale: analysis of 7,764 head injuries. **J Am Coll Surg** **199**:216–222, 2004
9. Eisenberg HM, Gary HE Jr, Aldrich EF, Saydjari C, Turner B, Foulkes MA, et al: Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. **J Neurosurg** **73**:688–698, 1990
10. Farahvar A, Gerber LM, Chiu YL, Carney N, Härtl R, Ghajar J: Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. Clinical article. **J Neurosurg** **117**:729–734, 2012
11. Farahvar A, Gerber LM, Chiu YL, Härtl R, Froelich M, Carney N, et al: Response to intracranial hypertension treatment as a predictor of death in patients with severe traumatic brain injury. Clinical article. **J Neurosurg** **114**:1471–1478, 2011 (Erratum in **J Neurosurg** **115**:191, 2011)
12. Ghajar J: Traumatic brain injury. **Lancet** **356**:923–929, 2000
13. Ghajar J, Hariri RJ, Narayan RK, Iacono LA, Firlik K, Patterson RH: Survey of critical care management of comatose, head-injured patients in the United States. **Crit Care Med** **23**:560–567, 1995
14. Guidelines for the management of severe head injury. Introduction. **J Neurotrauma** **13**:643–645, 1996
15. Härtl R, Gerber LM, Iacono L, Ni Q, Lyons K, Ghajar J: Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. **J Trauma** **60**:1250–1256, 2006
16. Härtl R, Gerber LM, Ni Q, Ghajar J: Effect of early nutrition on deaths due to severe traumatic brain injury. **J Neurosurg** **109**:50–56, 2008
17. Jennett B, Teasdale G, Galbraith S, Pickard J, Grant H, Braakman R, et al: Severe head injuries in three countries. **J Neurol Neurosurg Psychiatry** **40**:291–298, 1977
18. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C: Early indicators of prognosis in 846 cases of severe traumatic brain injury. **J Neurotrauma** **19**:869–874, 2002
19. Marshall LF, Becker DP, Bowers SA, Cayard C, Eisenberg H, Gross CR, et al: The National Traumatic Coma Data Bank. Part 1: Design, purpose, goals, and results. **J Neurosurg** **59**:276–284, 1983
20. McGraw CP: A cerebral perfusion pressure greater than 80 mm Hg is more beneficial, in Hoff JT, Betz AL (eds): **Intracranial Pressure VII**. Berlin: Springer-Verlag, 1989, pp 839–841
21. Narayan RK, Michel ME, Ansell B, Baethmann A, Biegon A, Bracken MB, et al: Clinical trials in head injury. **J Neurotrauma** **19**:503–557, 2002
22. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, et al: Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. **Lancet** **364**:1321–1328, 2004
23. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. **J Trauma** **30**:933–941, 1990
24. Sosin DM, Sniezek JE, Waxweiler RJ: Trends in death associated with traumatic brain injury, 1979 through 1992. Success and failure. **JAMA** **273**:1778–1780, 1995
25. Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM: Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. Clinical article. **J Neurosurg** **112**:1105–1112, 2010
26. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE: Traumatic brain injury in the United States: a public health perspective. **J Head Trauma Rehabil** **14**:602–615, 1999
27. Unterberg A, Kiening K, Schmiedek P, Lanksch W: Long-term observations of intracranial pressure after severe head injury. The phenomenon of secondary rise of intracranial pressure. **Neurosurgery** **32**:17–24, 1993

Manuscript submitted February 11, 2013.

Accepted August 7, 2013.

Please include this information when citing this paper: published online October 8, 2013; DOI: 10.3171/2013.8.JNS13276.

Address correspondence to: Jamshid Ghajar, M.D., Brain Trauma Foundation, 7 World Trade Center, 34th Floor, 250 Greenwich St., New York, NY 10007. email: ghajar@braintrauma.org.