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Revisiting the Effect Of Intracranial Pressure Variables in Predicting 28-Day Mortality in Traumatic Brain Injury Patients

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Abstract

Traumatic brain injuries (TBI) have a substantial individual and financial impact. Over the last three decades, intracranial pressure monitoring (ICP) has become part of standard clinical practice as both a predictor of TBI outcome and a critical care management tool. Despite national guidelines for ICP management, its use widely varies. Studies of ICP monitoring vary widely in their use and have limited analyses of ICP as a predictor of mortality. This study is a secondary analysis of data from a randomized clinical trial that provides excellent follow-up for evaluating ICP monitoring the first 48 hours of TBI as a predictor of 28-day mortality while adjusting for important demographic and clinical covariates.

The average opening ICP was less than 25 for those that died and the overall ICP values for 48 hours were below 20 for both survivors and non-survivors. Several summary measures of ICP values were evaluated using multivariate logistic regression and the average ICP measured over 48 hours was the only statistically significant predictor. Using ICP averaged for only 0-24 hours or 24-48 hours did not provide enough precision to achieve a statistically significant odds ratio. There were no quadratic or cubic relationships. The log of average ICP was also significant but did not yield a superior regression model.

Using the logistic regression, a probability plot representing borderline cases highlighted the importance of the Glasgow Coma Scale, evidence of brain herniation on admission computerized tomography and age greater than 40 as important predictors of 28-day

mortality. Though the plot was extrapolated to average ICP values of 78 mmHg, all but one patient had average ICP values less than 40mmHg. ICP averaged over the first 48 hours of monitoring was an independent predictor of 28-day mortality after adjusting for covariates. For every mmHg increase in ICP, there was an 8% higher risk of 28-day mortality. The findings of this study are relevant to TBI patients that have ICP aggressively monitored and managed to keep ICP below 20 mmHg, and might not generalize to a wider population of TBI patients.

Introduction

Significance of traumatic brain injury

The Center for Disease Control (CDC) estimated that, from 1995-2001, there were 1.4 million traumatic brain injuries (TBI) per year with 50,000 fatalities and 235,000 hospitalizations. In 2002 for 12 states, the incidence of hospitalization for TBI patients was estimated at 79.0 per 100,000 population with 6% dying in the hospital and 20% discharged to other facilities or with home services [1].

The economic impact of TBI in 1985 was estimated at $37.8 billion, not including the pain and suffering to victims and families. Direct costs were estimated at $4.5 billion for medical care and $20.6 billion for loss of work and disability. $12.7 billion was attributed to loss of potential income due to premature death[3].

In the 1970's and 1980's, the annual incidence of TBI was estimated at 200 per 100,000 with a range of 132 to 367 per 100,000. From 1980 to 1994 there was a 20% reduction in TBI associated deaths from 24.7 per 100,000 to 19.8 per 100,000. In 1994, data from seven states (Arizona, Colorado, Minnesota, Missouri, New York (excluding New York City), Oklahoma and South Carolina) reported that for TBI deaths, 16.9% died prior to hospital admission. Among those hospitalized, 5.6% died during the acute phase of care. The overall TBI related death rate was 20.7 per 100,000[3].

In light of the catastrophic potential of TBI, many studies have attempted to identify prognostic variables in hopes of improving patient outcomes. Among the many

physiological and summary variables used, intracranial pressure (ICP) has been used widely. Initial studies on ICP date back to the 1970's. At that time, very high ICP values, usually greater than 40 mmHg, were associated with a very high likelihood for brain death and such ICP measurements were used as an indication to stop further treatment. Later, ICP monitoring was used for guiding pharmacologic and ventilator therapy with the goal of assuring adequate cerebral blood flow in the critical care management of TBI patients.

Physiopathology of traumatic brain injury and ICP

The brain is a highly metabolic organ and consumes about 20% of the total oxygen body requirement. Brain metabolism is supported by sufficient cerebral arterial blood flow. Brain perfusion is limited by cardiac output, ICP, and venous intracranial. The Monroe-Kelly principle states, "increased brain tissue volume displaces cerebral spinal fluid (CSF) or the cerebral blood volume." The total intracranial volume of an intact skull is made up of brain tissue, CSF, intravascular blood and other mass such as air, blood clots or edema. If TBI results in brain tissue swelling, then CSF or blood will be displaced or all intracranial contents will experience higher pressures, potentially reducing cerebral blood flow and causing neuronal injury.

Normal ICP is 0 to 10 mmHg. Over half of patients with TBI have elevated ICP [8]. Little information exists on the clinical significance of ICP values ranging from 11 to 20mmHg. ICP greater than 20 mmHg may result in cerebral ischemia due to direct pressure-dependent reduction in cerebral blood-flow. One of the largest prospective

observational studies that evaluated the prognostic value of ICP found the optimal starting point to be 20 mmHg. In a case series of 195 elderly patients, there was a higher death rate at 72 hours and 6 months among patients admitted with ICP>20 mmHg compared with to patients with ICP <20mmHg. In that case series at 6 months follow-up, 75% of the 195 patients had died whereas among those with elevated ICP, 90% died [4]. In another series, almost all patients with ICP> 40mmHg in the first 48 hours died [5]. TBI patients with ICP over 20 mmHg have worse neurological outcomes based on Glasgow Outcome Scales (GOS) [6] and higher mortality rates[7].

ICP monitoring has enjoyed widespread use but the effectiveness of controlling ICP with various interventions has not been demonstrated in randomized clinical trials [8]. In the 1970's the mortality rate of TBI was estimated to be 55% and the use of ICP monitoring was believed to reduce mortality to as low as 28%. Since 1995, the Brain Trauma Foundation has recommended ICP monitoring as part of the management of TBI patients but a recent report demonstrates a wide variability with the use of ICP monitoring. The same report demonstrated a statistically significant difference in mortality based on the prevalence of ICP monitoring[9]. This was a retrospective study of 34 academic hospitals divided by ICP monitoring >50% use (aggressive) or <50% use (non-aggressive) in TBI patients with Glasgow Coma Scale (GCS)<= 8 and significant CT findings, the aggressive group had an improved mortality of 27% compared to 45% for the non-aggressive group[9].

The proportion of patients with severe ICP elevation that have poor outcomes has been high despite interventions [10] such as mannitol, hypertonic saline, CSF drainage and surgical decompression[11]. In earlier studies, pediatric and adult patients with ICP>20 mmHg but not reducible with interventions, mortality was similarly high[12], [13].

Management of raised ICP

Interventions to reduce ICP are numerous. Surgical decompression by removing part of the skull and masses such as a hematoma or swollen dead brain tissue can reduce ICP but closure and surgical inflammation may become a problem. Pharmacologic interventions include infusion of hyperosmolar solutions such as mannitol and hypertonic saline solutions to try to reduce interstitial and intracellular water volume of brain tissue through osmosis. However, physiologic limits of serum osmolarity limit this therapy. Temporary reductions in ICP can be achieved by hyperventilating intubated patients until the arterial tension of carbon dioxide ($PaCO_2$) is approximately 30 mmHg. This uses a mechanism called cerebral autoregulation that regulates cerebral arterial dilation by $PaCO_2$. Reducing the $PaCO_2$ causes cerebral vasoconstriction, reducing blood volume in the skull and potentially reducing ICP. Hyperventilation is a temporary measure that achieves its effect for several hours before accommodation occurs. Similarly, cerebral spinal fluid (CSF) can be drained to reduce the volume in the skull and thus reduce pressure. To minimize ischemic injury in the presence of elevated ICP where cerebral perfusion may be compromised, metabolic effects such as hypothermia, barbiturates or sedation and muscle relaxants have been employed to minimize oxygen dependent metabolism and thus salvage injured neurons.

Alternatively, cerebral perfusion pressure (CPP) can be improved, despite elevated ICP, by increasing the MAP using cardiac drugs. Single or combination therapy of dopamine, norepinephine with dobutamine, phenylephrine or epinephrine infusions are often titrated to maintain a CPP of 60 mm Hg but this can be taxing to the heart, particularly in patients that cannot tolerate tachycardia or increased ventricular wall strain due to heart disease. These drugs also may cause problems with homeostasis by causing sympathetic stimulation of the gastrointestinal tract, causing excessive vasoconstriction. This would reduce blood flow and may result in gastrointestinal failure with impaired absorption of nutrients that are usually given by an oral- or nasal-gastric tube.

Association between ICP and outcome

Secular trends in management suggest a reduction in mortality [9], [14], with some evidence supporting greater use of ICP monitoring. As mortality improves, greater attention is being given to understand the consequential disabilities of TBI. It is estimated that 90,000 people annually have disabilities due to TBI, giving an estimated prevalence of 5.3 million[3].

There are a wide variety of studies, most of which are retrospective and often with varying criteria and statistical methods. Some of the more common factors that appear to have predictive value include age, elevated ICP, midline brain shift and the GCS. Studies in surgical trauma without distinction for TBI have found variables such as Trauma Score, Injury Severity Score (ISS), arterial blood base deficit, and the presence of

comorbidities to predict mortality. Age and comorbidities, however, interact in such a way that the greater the age the less the effect of the comorbidities. ICP is one of the earliest physiological variables that has been used widely for management of TBI patients. National guidelines recommend ICP monitoring in TBI patients[9].

Statistically, most studies lack a rigorous approach. Most studies on TBI patients and ICP have used univariate stratification to evaluate the predictive value of variables. One case-series of 110 TBI patients controlled for multiple physiologic variables within the first 72 hours. However, only ICP elevation was significant to predict one-year survival[15]. No improvement in the model was gained by adding arterial blood pressure, cerebral perfusion pressure (CPP), arterial O_2 saturation (SaO_2), temperature, and heart rate.

ICP monitoring has recently been called into question by an observational study evaluating 685 consecutive TBI patients divided between Hospital B that uses ICP monitoring vs. Hospital A that does not use any ICP monitoring[16]. They attempted to evaluate the use of ICP monitoring vs. no ICP monitoring since Hospital B had ICP monitoring available and Hospital A did not have ICP monitoring available. There were no differences in mortality or 12-month GOS scores. However, near statistically significant differences in the two groups suggest the Hospital B had patients with more hypotension, anemia, and diffuse axonal injury. Although 67% of patients in Hospital B received ICP monitoring, there were only 27% of the patients with elevated ICP >20. Moreover, no evaluation was made for patient with elevated ICP that improved with intervention. It would be beneficial to further investigate the value of ICP monitoring.

Raised ICP has been consistently associated with poor neurological outcome or death in patients with TBI. A large body of literature in the form of clinical experience or cohort studies is available, with few comparative studies. Thus far, no large studies evaluated the independent effect of ICP measurements in predicting outcome in brain injury patients. Several risk factors reportedly contribute to mortality in patients with TBI including hypoxia, hypotension, hyperthermia, admission GCS, and main intracranial diagnosis as indicated by findings on head computed tomography (CT). Secular trends in the management of TBI and aggressive ICP management suggest a beneficial effect on outcomes. Further understanding of the role of ICP monitoring and ICP management with aggressive therapy needs to be elucidated. It is important to quantify the association between ICP and long-term outcomes to determine if ICP values or trends may help guide clinical and ethical decision-making in TBI patients being provided care in neurosurgical intensive care units.

ICP management continues to be a strong component of TBI patient management in neurosurgical ICUs. At Harborview Medical Center (Seattle, WA), ICP elevation has been treated aggressively. This study evaluated the various aspects of ICP in the first 48 hours of monitoring to predict 28-day mortality. Multivariate statistics were used to control for potential confounding variables.

Specific Aims

The primary aim of the present study was to evaluate different ICP patterns and values measured within the first 48 hours of placement of ICP monitoring in TBI patients to determine the independent effect of ICP on 28-day mortality.

Hypothesis:

The estimates of the odds ratios of death for ICP measurements modeled according to a priori specified definitions (see methods section) were equal to one, indicating that ICP is not different among TBI patients with normal or abnormal ICP, after accounting for covariates known to be important predictors of TBI outcome.

Methods

Design

This secondary analysis used prospectively collected data from a randomized clinical trial comparing intravenous magnesium and intravenous normal saline placebo in patients with moderate to severe TBI. These patients were admitted to Harborview Medical Center, (Seattle, WA), a Level I regional trauma center, between August 1, 1998 and October 31, 2004. This trauma center has patients managed jointly by neurosurgeons and a neurointensivist. In this setting, ICP monitoring is aggressively used and abnormal ICP over 20 mmHg is treated aggressively. This study evaluated different ICP variables to determine a clinically useful aspect of ICP measurement that predicts 28-day mortality in TBI patients.

These data provided a good quality dataset with near complete follow-up that could be used for 28-day mortality. Only 8 families (<2%) refused consent for the study prior to randomization. Eight cases withdrew consent for continued treatment, primarily due to loss of IV access. This resulted in 499 patients with over 99% follow-up for mortality by 28 days and 93% follow-up through 6 months. This secondary analysis includes all eligible patients who were randomized and, after applying additional inclusion and exclusion criteria, evaluated 28-day mortality as the outcome.

The original study intervention consisted of an initial intravenous (IV) loading dose of magnesium sulfate or identical-appearing saline administered over 15 minutes within 8 hours of injury and followed by a continuous infusion to maintain magnesium levels in

the target range for 5 days. The research pharmacist adjusted the infusion rate daily according to an algorithm based on the magnesium level that day and the target level. The original publication did not show any effect from magnesium therapy group on mortality or neuropsychological outcomes and is presently in peer-review for publication (personal communication with Dr Temkin, 2006). This secondary analysis adjusted for the effect of magnesium therapy vs placebo in a blinded fashion.

Inclusion Criteria

Patients were included if they had depressed consciousness as rated on the GCS with a score of 3-14, or if intubated, with a motor GCS of 1-5 without pharmacologic muscle relaxation, or intracranial surgery within eight hours of head injury or resuscitation. For this study all patients must have had ICP monitoring within 12 hours from traumatic brain injury to the first measurement. The minimum age of inclusion was age 18 years.

Exclusion Criteria

Patients must have been admitted within 8 hours of injury. Patients were excluded if they sustained a penetrating wound to the calvarium. Patients were excluded if they had open cranium fractures, did not receive the study drug within 8 hours of injury, had evidence of renal insufficiency based on a serum creatinine over 2.0 mg/dl, were pregnant, were prisoners, or were known to live overseas and or were otherwise unavailable for follow-up. Patients were excluded for a declaration of brain death or an Abbreviated Injury Score (AIS) of 6. This study excluded 12 patients that had penetrating TBI and an additional 12 who had cardiovascular death within the 48 hours.

Measurements of ICP

ICP was modeled according to a priori specified criteria. Normal ICP was defined as ICP of 0-20 mmHg during the first 48 hours of monitoring, and this range was used as the reference category for all analyses.

1. ICP average: The mean of ICP measurement for 48 hours.

2. The area under the curve (AUC) of the first 48 hours of ICP measurements that exceeded a series of cutoff values was estimated using the trapezoid rule.

3. ICP AUC trend: Using the AUC for Day 1 over the AUC for Day 2, a ratio was determined for ICP trend between days one and two. A ratio >1 indicated a lowering of ICP from day 1 to day 2. A ratio <1 indicated an increase in ICP from day 1 to Day 2. A ratio of 1 indicated both days had overall equivalent ICP values.

4. ICP opening pressure: the initial ICP measurement.

5. Initial ICP to the minimum ICP value: The magnitude of the difference from the opening ICP pressure to the lowest ICP pressure in 48 hours.

6. Initial ICP to the maximum ICP value: The magnitude of the difference from the opening ICP pressure to the largest ICP pressure in 48 hours.

7 Last ICP is the ICP measurement last measured at the end of the 48-hour monitoring period. If ICP monitoring was stopped prior to 48 hours, the last measurement available was carried out to 48 hours.

Measurements

A research nurse used a standardized intake form and retrieved clinical data from a computerized information system (CIS). ICP measurements were taken using an intraparenchymal pressure monitoring device, which has a pressure transducer that continuously measures ICP waveform. ICP values were scheduled to be collected on an hourly basis but additional values were included if there were any meaningful changes.

The initiation and continuation of ICP monitoring was based on clinical decisions by the attending neurosurgical admitting service at Harborview Medical Center. The time for initiation of ICP monitoring varied with each patient and did not necessarily coincide with therapeutic interventions to control elevated ICP. Since our inclusion criteria for the secondary analysis required a 12-hour maximum duration from the traumatic injury to first ICP monitoring, therapeutic interventions at most were started 12 hours ahead of ICP monitoring. However, therapeutic interventions to lower ICP are, in practice, only used with monitoring available to guide therapies.

Follow-up for death was achieved by one, three and six month patient interviews and surveys. The survey consisted of direct contact with patients. If patients could not be contacted, alternate methods such as checking credit bureau reports and county records were used.

Assumptions of ICP measurements

It was assumed that small or short elevations in ICP values that were associated with coughing due to tracheal irritation were not recorded as such by nursing to avoid excessively high ICP values being recorded for reasons that were brief and unlikely to contribute significantly to the overall effect of intracranial hypertension on cerebral perfusion. However, the original clinical study did not attempt to evaluate nursing practices for inter-nurse consistency.

Calculation for area under the curve (AUC)

To approximate the integral of the curve of the ICP trendline for each patient, the AUC was calculated by the trapezoid rule using the formula $0.5*(\text{hour}_{i+1} - \text{hour}_i)* (\text{ICP}_i + \text{ICP}_{i+1})$. Each trapezoid measurement was made for ICP that exceeded the predetermined series of ICP cutoff, which was set to 20 in this study. The units of AUC was in mmHg*time and for the main logistic regression, it was converted back to mmHg.

Treatment of missing data or changes in ICP

If there were three or more hours of consecutive missing data, and then ICP monitoring was resumed, no interpolation was made to include these gaps, reducing sampling time to less than 48 hours. This three-hour criterion was used to avoid erroneously weighting the calculation of the AUC to values adjacent to these gaps.

Treatment of ICP data during surgery

ICP measurements, that were recorded during operative procedures and made available to the original nurse data collector, were treated similarly to all their available ICP values in the first 48 hours. The rationale for using the ICP values of patients undergoing surgery was that such ICP values are indicators of valid pathophysiological effects on cerebral perfusion.

Treatment of ICP monitoring that is terminated in less than 48 hours:

When ICP monitoring is discontinued prior to 48 hours not because of death, the last value will be carried forward until the completion of 48 hours. This practice is applied under the assumption that ICP monitoring was discontinued because of patient improvement, which clinically is the routine practice to minimize risk of infection. This helps to weight the ICP values through the 48-hour monitoring period to reflect the clinical improvement, particularly if elevated ICP values occurred only in the initial period of monitoring.

Covariates

The covariates were selected for their potential clinical relevance to ICP and the outcome and are given below:

Age (dichotomous): Patients were divided into an older age group >40 and the reference younger group <= 40 years old to provide a clinically useful categorization in understanding the effect of age in the model.

Hypoxia as measured by the first available pressure of arterial oxygen tension (PaO2) by arterial gas analysis. Hypoxia was coded as present indicated by a value of 1 if the PaO2 was less than 60 mmHg.

Glasgow Coma Scale (GCS): This is a validated scale used to evaluate the depth of coma based on physical indications of eye, verbal and motor evaluation. The scale range from 3 (most severe) to 15 (normal).

Drug: The drug and normal saline placebo groups were coded as a 1 or 2, but we were blinded to the actual assignments.

AIS Abbreviated Injury Score: this is a validated scoring system used to evaluate the severity of trauma. The score can range from 1 (minor injury) to 6 (unsurvivable). The higher the score the worse the injury. Patients with a score of six were excluded in the study

Herniation: based on computerized tomography findings of brain herniation; dichotomous, where 0 is no herniation and 1 is evidence of herniation.

Baseline MAP: Mean arterial pressure averaged from the first three hours of hospital admission. This is a continuous variable.

Surgical Decompression: dichotomous variable where 1 indicates surgical decompression was performed within the first 24 hours. This was selected as a covariate for its clinical value as a measure of therapeutic need.

The original study used the Therapeutic Intensity Level (TIL), a summary variable for therapeutic interventions. However, the TIL does not account for differences in the magnitude or frequency of each therapy. Surgical decompression was used as a surrogate measure.

Only four patients had bilaterally fixed pupils and no data were available for unilaterally fixed pupils so data on pupils were not used in the analyses.

Statistical Methods

Data were summarized using descriptive statistics and measures of central tendency. Initially, a logistic regression model was fitted using all the selected covariates without any ICP variables. A correlation matrix was used to evaluate the correlation among the possible ICP variables. When ICP variables were highly correlated with Pearson's $r > 0.9$, one of the two variables were removed and the other variable was used as the representative measurement for the analysis. Multivariate logistic regression was used to estimate the predictive value of various ICP measurements for 28-day mortality.

Model building procedure

Each ICP summary measurement was individually evaluated using logistic regression with all the covariates and, subsequently an interaction term using the respective ICP variable and surgical decompression was added with the main terms in model.

A final full logistic regression model using all the ICP variables was determined and then in a backward stepwise iterative process, the Wald statistic was used to compare the main effects of each ICP variable. The ICP variable with the largest p value for the Wald statistic was removed and the entire process was repeated. This continued until a reduced model with only significant Wald statistics for the ICP main effects were maintained in the reduced model while controlling for clinically relevant covariates. Models including an interaction term between the ICP variable and each prognostic variable were also fit. Finally, we compared models that used different scalings of the ICP measure, including quadratic, cubic, and log ICP measures.

A predicted probability plot of 28-day mortality by ICP values was fitted using meaningful case scenarios of covariate settings. For covariates that were continuous, the mean sample values were use. Variations were systematically made for age category, herniation category and GCS to demonstrate the estimated probabilities for this sample population.

Results

Descriptive and univariate Statistics

Overall, a total of 341 patients remained in the dataset after additional inclusion and exclusion criteria were applied. Table 1 itemizes the patients that were included and excluded from the original 499 patients to the final group. The majority of patients died in the first 28 days.

Table 1. Patient Loss

Time	Death/Loss/Excluded	Patient Balance
Start of study, patients randomized		499
Excluded for late loading of magnesium	1	483
Excluded for age less than 18 years	51	426
Excluded for ICP bolt placed >12hrs	50	409
Excluded for more than one of reasons above	28	369
Excluded for penetrating head injury	12	357
Deaths within 48 hours of admission	12	345
Missing GCS‡	2	343
Lost to follow-up before 28 days^	2	341
Died		
	Deaths	Survivors
48 hours to 28 days	51	290

^ patients 3260 and 3408

‡ Patient 3116 and 3149 excluded for lack of GCS data

Within the first 48 hours, twelve patients died and these were excluded since these patients died during the 48 hour ICP monitoring period. Two patients were missing GCS data and were thus excluded. Two patients were discharged within 28 days post-injury and were lost to follow-up, resulting in a 0.7% loss to follow-up.

Of these two patients lost to follow-up, one was in the magnesium group and one patient was assigned to the placebo group . One patient was a 36-year old male with an opening ICP of 15 and discharged at day 19. The other patient was a 58-year old male with an

opening ICP of 2.8 and was discharged at day 12. Data on these two patients were discarded, giving a total population of 341. A total of 51 of the final sample of 341 patients (15 %) died within days 2 to 28.

The first 48 hours of ICP monitoring was used as the critical window for predicting outcomes. The mean interval between ICP measurements was .34 (0.09) hrs, giving an average measurement of at least one ICP measurement every hour. The fact that the duration was on average every 20 minutes indicates that there were many changes occurring in ICP values. ICP averages for days one and two were, respectively, 15.1 (7.2) and 15.2 (9.5). No upward or downward pattern was found between days one and two. The ICP ratio for trends was not used for further multivariate analysis.

Table 2 provides the demographics, covariates and ICP variables for all patients and subdivided into survivors and non-survivors. The drug and placebo groups are approximately equally distributed. For continuous variables, the independent Student's t-test was used to evaluate the difference of the means divided by either survivorship (see Table 2) or average ICP split at 20mmHg (See Table 3). For categorical variables, the Chi-square analysis was applied to evaluate the difference of the two groups. The majority of patients were white males age 40 or less. Non-survivors tended to be older than 40 years, had more evidence of herniation ($p<0.001$), pre-admission hypoxia ($p<0.05$), and receiving surgical decompression ($p<0.01$).

The estimates of the covariates were used later for the probability plots. For the average ICP over 48 hours, the values ranged from 2.1 to 72.8 with the 25th, 50th and 75th percentiles being, respectively, 10.3, 14.4 and 18.2.

Table 2. Patients characteristics all and subdivided by survivorship

Variable	All patients (n=341)	Survived (n=290)	Died (n=51)
Categorical Demographics and Covariates			
Magnesium vs placebo group (n) [ns]	178 vs163	147 vs 143	31 vs 20
Frequency of Age >40 n (%)*	124 (36%)	99 (34%)	25 (49%)
Male n (%)[ns]	262 (77%)	226 (78%)	43 (84%)
White n (%)[ns]	267 (78%)	224 (77%)	44 (86%)
CT indication of Herniation n (%)**	206 (60%)	162 (56%)	44 (86%)
Hypoxia n (%)*	89 (26%)	70 (24%)	19 (37%)
Surgical decompression n (%)**	104 (31%)	80 (28%)	24 (47%)
Count of Mean ICP abnormal n (%)	52 (15%)	36 (12%)	16 (31%)
Continuous/Interval Covariates			
Age in years mean (SD)	36.6 (16)	35.7 (15.6)	41.9 (17.5)
Lowest GCS[§] mean (SD)	6.3 (2.5)	6.6 (2.5)	4.1 (1.5)
Hypoxia (PaO2[Δ]) mean (SD)	48.5 (11.7)	48.3 (10.8)	49.2 (14.7)
AIS head mean (SD)	4.5 (0.6)	4.5 (0.6)	4.8 (0.5)
Mean first 3 hrs of MAP mean (SD)	124.0 (15.9)	124.1 (15.2)	122.9 (19.5)
Continuous Differing ICP variables mean (SD)			
Average ICP over 48 hours[†]	14.6 (6.3)	14.0 (5.3)	18.1 (9.7)
First ICP	17.8 (11.8)	16.9 (10.9)	23.0 (15.2)
Baseline ICP to Min ICP in 48 hours	11.5 (11)	10.8 (10.2)	15.5 (14.1)
Baseline ICP to Max ICP in 48 hours	14.7 (14.4)	14.5 (14.4)	15.7 (14.1)
AUC[‡] cutoff 20	376.6 (535.3)	314.2 (446.9)	713.5 (802)
Last ICP in 48 hours	14.7 (8.2)	14.1 (7.4)	17.5 (11.1)

[§] Lowest GCS in 24 hours. 4 cases missed lowest GCS so the Emergency Room GCS was used.

[Δ] PaO2: Arterial oxygen pressure in mmHg

[†] For the average ICP over 48 hours, the values ranged from 2.1 to 72.8 with the 25th, 50th and 75th percentiles being, respectively, 10.3, 14.4 and 18.2.

[‡] AUC cutoff: Area under the curve for elevated ICP over criteria of 20 mmHg monitored for 48 hours.

*, ** n comparing survivors and non-survivors: * p<=0.05, **p<=0.01

ns: non-significant p value (0.05)

Confounding

Table 3 was created to evaluate the difference in demographics and characteristics when patients were divided by the categorical variable of normal vs abnormal average ICP. Tables 2 and 3 can be combined to evaluate for confounders, which would be those variables associated with both the outcome, 28-day mortality and the predictor average ICP. Herniation and GCS were statistically associated with average ICP <=20 mmHg and mortality, indicating that they are confounders in these data.

Table 3 Patient characteristics and ICP variables subdivided by normal or abnormal average ICP

Variable	Average ICP <=20 (n=289)	Average ICP >20 (n=52)
Categorical		
Magnesium vs placebo group (n) [ns]	146 vs 143	32 vs 20
Frequency of Age >40 n (%)[ns]	106 (37%)	18 (35%)
Male n (%)[ns]	220 (76%)	42 (81%)
White n (%)[ns]	227 (79%)	40 (77%)
CT indication of Herniation n (%)*	168 (58%)	38 (73%)
Hypoxia n (%)[ns]	77 (27%)	12 (23%)
Surgical decompression n (%)[ns]	88 (30%)	16 (31%)
Continuous		
AIS [ns]	4.5 (.6)	4.6 (.5)
GCS*	6.4 (2.5)	5.4 (2.4)
Baseline MAP [ns]	123.3 (15.8)	127.7 (15.9)
Baseline ICP*	15.9 (10.0)	28.9 (15.1)
Baseline ICP to Min ICP*	10.5 (9.9)	17.1 (14.5)
Baseline ICP to Max ICP*	13.8 (14.1)	19.4 (14.9)
Last ICP*	13.0 (6.8)	24.0 (8.9)
Average ICP*	12.9 (4.1)	24.3 (7.7)

* p<=0.05 for chi square or independent t-test assuming unequal variances.
ns: non-significant p value (0.05)

Table 4 provides a correlation matrix of the ICP variables. Of these variables, the baseline ICP was highly correlated with the magnitude of the difference between the baseline ICP and the lowest ICP value with Pearson's r at 0.91 ($p<0.01$). Therefore, the magnitude of the difference between the baseline ICP and the lowest ICP value was removed from further analysis.

Table 4 Correlation matrix of Pearson's r for differing ICP values

Variable	Base ICP	Baseline ICP -min	Baseline ICP-max	Last ICP	AvgICP	AUC ICP 20
Baseline ICP	1	0.92**	-0.25**	0.29**	.42**	0.51**
Baseline ICP-min		1	-0.31**	0.05	.12*	0.27**
Baseline ICP-max			1	0.24**	.24**	0.26**
Last ICP				1	.74**	0.58**
AvgICP					1	.83**
AUC ICP 20						1

* $p \leq 0.05$
** $p \leq 0.01$
Baseline ICP: First ICP measurement recorded
Baseline ICP-min: Magnitude of baseline ICP to Minimum ICP value 0-48 hours
Baseline ICP-max: Magnitude of baseline ICP to Maximum ICP value 0-48 hours
Last ICP: Last ICP value recorded within 48 hours
AvgICP: ICP averaged over 48 hours.
AUC ICP 20: AUC of ICP above 20 mmHg in the first day in mmHg*hours

Logistic Regression

The logistic regression models including the covariates were evaluated for each of the ICP variables. Only average ICP measured over 48 hours was statistically significant ($p<0.05$). All regression models adjusted for all eight covariates. Evaluating the eight covariates alone, GCS, herniation and age categories remained statistically significant ($p<=0.05$) in all models (see Table 5). Examining the odds of mortality for the covariates alone, patients older than 40 years had 2.2 times the risk compared to a person less than 40 years old. Patients with herniation had 4.4 greater odds for death than patients without herniation and, for every increase in GCS, patients had a 58% lower chance of mortality. None of the interaction terms between an ICP variable and a covariate demonstrated statistical significance.

Table 5. Logistic regression of covariates without ICP in the equation

Covariates only	Odds Ratio and [95% CI]
Age <=40 years old	1
Age >40 years old	2.16 [1.06, 4.38]
No hypoxia (PaO2>=60 mmHg)	1
Hypoxia (PaO2<60 mmHg) present	1.49 [0.72, 3.08]
Glasgow Coma Scale*	0.58 [0.48, 0.70]
No CT finding of brain herniation	1
CT finding of brain herniation	4.43 [1.69, 11.60]
No surgical decompression	1
Surgical decompression in first 24 hours	1.15 [0.54, 2.43]
Drug group 1 or 2†	0.82 [0.41, 1.68]
AIS score ‡	1.68 [0.84, 3.35]
Baseline Mean Arterial Pressure (MAP)	1.00 [0.98, 1.03]

Δ PaO2: Arterial oxygen pressure in mmHg

*Glasgow Coma Scale ranges from 3-14 in this study. As the score increases, the odds of mortality decreases by 58%

† Drug group 1 and 2 are blinded code assignments for either placebo or magnesium therapy

‡ AIS (Abbreviated Injury Score) can range from 1 (minor injury) to 6 (unsurvivable). For this study this group ranged from 3 to 5. For every point the score increases from 3 to 5, the injury poses a greater threat to life. For every point above 3, the odds of death increases by 68%

Average ICP over 48 hours (two days) was compared to one day measurements (ICP measured from 0 to 24 hours and then with 24-48 hours) using the same logistical regressions. Neither one-day measurements provided statistically significant estimates. Because single day ICP averages did not demonstrate a significant relationship with the outcome, they were not further considered as indicator variables

Table 6 provides the logistic regression model using all the covariates and ICP variables and then a reduced model. In the reduced model, a stepwise backward iterative elimination process was used which removed a single ICP variable with the largest non-significant p values ($p>0.05$). Only average ICP over 48 hours remained statistically significant. In the reduced model, for every increase in average ICP measured over a 48-hour period, there is an 8% increase in the risk of 28-day mortality.

Table 6. Logistic regression of covariates and multiple ICP variables.

Variable	Full Model OR [95% CI]	Reduced Model OR [95% CI]
Age category	2.24 [1.06, 4.73]	2.22 [1.07, 4.62]
Drug or placebo	0.86 [0.41, 1.80]	0.87 [0.42, 1.80]
Herniation	3.70 [1.36, 10.01]	3.65 [1.37, 9.71]
Hypoxia	1.58 [0.73, 3.39]	1.67 [0.79, 3.52]
Abbreviated Injury Score	1.66 [0.81, 3.40]	1.63 [0.80, 3.34]
Glasgow Coma Scale	0.59 [0.49, 0.73]	0.60 [0.49, 0.72]
Baseline MAP	1.00 [0.98, 1.03]	1.00 [0.98, 1.02]
Surgical decompression	1.44 [0.64, 3.26]	1.43 [0.64, 3.20]
Average ICP	1.06 [0.94, 1.20]	1.08 [1.01, 1.15]
Baseline ICP	0.99 [0.96, 1.03]	-
Baseline ICP to Max ICP	0.98 [0.95, 1.01]	-
Last ICP	1.00 [0.93, 1.06]	-
AUC 20	1.00 [1.00, 1.00]	-

The full model was reduced in a backward stepwise approach by removing the ICP variable with the largest p value. This resulted in removal of the following: Last ICP at 48 hours (p .886), Baseline ICP (p=.617), AUC 20 (p=.635), and Baseline to Maximum ICP (p=.259).

Using the reduced logistic regression model of average ICP with all eight covariates, eight separate regression models were evaluated using one interaction term between a covariate and the ICP variable (see Table 7) in the reduced model (see Table 6). None of the terms were statistically significant ($p>0.05$), so the interaction terms were left out from the final reduced model.

Table 7. Interaction terms evaluated separately with the ICP averaged over 48 hours and all the covariates and the main terms included in the model

Interaction variables run separately	P value for Wald statistic
AVGICP by Age category	.248
AVGICP by drug or placebo group	.456
AVGICP by herniation category	.620
AVGICP by hypoxia category	.399
AVGICP by Abbreviated Injury Score	.475
AVGICP by Glasgow Coma Scale	.561
AVGICP by Baseline Mean Arterial Pressure	.546
AVGICP by Surgical decompression category	.693

AvgICP: ICP averaged over 48 hours.

Table 8 evaluated the average ICP variable to check for quadratic, cubic or logarithmic relationships. The logarithmic equation was significant. However, comparison of the deviance using the all the covariates and either ICP or log ICP demonstrated that both models appeared similar, with likelihood (?) ratios, respectively, of 204.1 and 204.8. For pragmatic reasons, average ICP was selected and log average ICP was dropped. Evaluation of the potential for a quadratic and cubic relationship had no effect on the odds ratio or its significance.

Table 8. Alternate Scaling of ICP measures

AVGICP OR [95%CI]	$AVGICP^2$ OR [95%CI]	$AVGICP^3$ OR [95%CI]
1.08 [1.01, 1.15]	-	-
1.09 [0.93, 1.28]	1.00 [1.00, 1.00]	-
1.11 [0.73, 1.69]	1.00 [0.98, 1.02]	1.00 [1.00, 1.00]
LOGAVGICP	-	-
13.30 [1.40, 126.27]	-	-

Figure 1 gives the probability plot for ICP ranging from 10 to 78 for various case scenarios. The predicted probability of death was plotted for differing common patient profiles given as cases 1 through 8. The final reduced logistic regression for the probability plot using the constant and beta values for the model incorporated average ICP over 48 hours with all covariates. Interaction terms were not included since there were no significant interaction terms for any of the models (see Table 7). It is important to note that although the plot is extrapolated to average ICP values of 78 mm Hg, all but one patient had average ICP values less than 40 mm Hg. Therefore, interpretation of the plots should be limited to average ICP from 10 to 40 mm Hg.

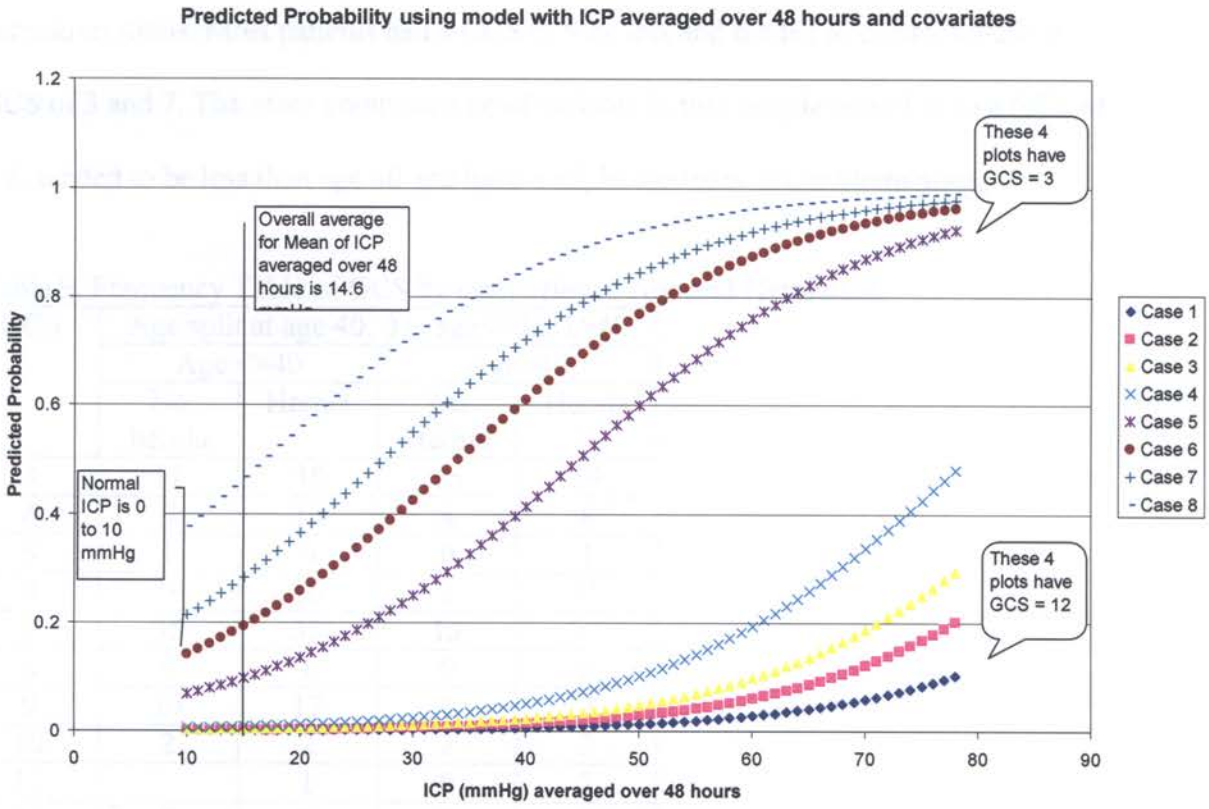
For these plots, the covariates drug was set to 1 arbitrarily since there was an approximately equal distribution between the two groups and we were blinded to the assignment of magnesium or placebo therapy. Hypoxia was set to 0 since the majority of patient (74%) did not have evidence of pre-admission hypoxia. AIS and baseline MAP were set to the mean values for the entire sample. A comparison between surgical decompression and no surgical decompression demonstrated very little difference in the probabilities so surgical decompression was set to 0.

The calculation for predicted probability for each value of ICP is

Eta = -4.1 + 0.797*(Age category) - 0.139*(Drug set to 1) + 1.296*(Herniation category)
+ 0.511*(Hypoxia category set to 0 for no hypoxia) + .489*(AIS set to 4.5)
- 0.519 (GCS) + .002*(Baseline MAP) + 0.360 *(Surgical decompression set to 0)
+ .075*(Average ICP ranging from 2 to 78).

The predicted probability is Exp(Eta)/(1+ Exp(Eta))

Figure 1 Predicted probabilities for average ICP 10 to 78 mmHg*



	Age category‡	Herniation category$^{\Delta}$	GCS†
Case 1	0	0	12
Case 2	1	0	12
Case 3	0	1	12
Case 4	1	1	12
Case 5	0	0	3
Case 6	1	0	3
Case 7	0	1	3
Case 8	1	1	3

†Glasgow Coma Scale: numeric score for severity of coma (3: most severe, 15: no coma)

‡ Age: 0 <=40 years old, 1 >40 years old

$^{\Delta}$ Herniation CT findings of brain herniation (0; none, 1: evidence of herniation)

* It is important to note that the probabilities from average ICP of 40 and to 78 are extrapolated. Only one patient had an average ICP above 40.

Surgical decompression within the first 24 hours and was set to 0.

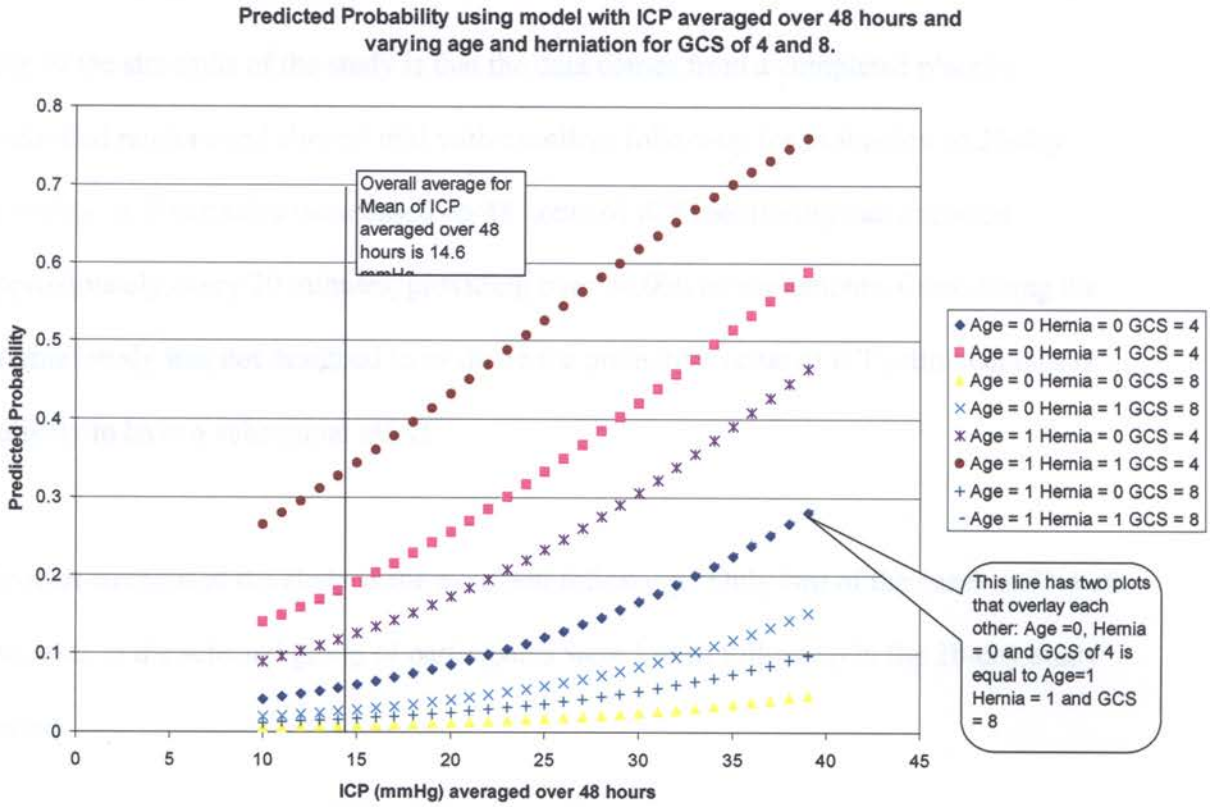
Table 9 provides a frequency distribution of patients based on GCS score, age and herniation status. Most patients had a GCS of 9 or less and tended to cluster around a GCS of 3 and 7. The more common type of patients in this sample would have a GCS of 3-8, tended to be less than age 40 and have a slight tendency toward herniation.

Table 9. Frequency Table of GCS by categories of Age and Herniation

GCS	Age split at age 40; 0 is age<=40, 1>40			
	Age <=40		Age>40	
	No hernia	Hernia	No Hernia	Hernia
3	11	35	15	19
4	9	18	4	8
5	1	0	0	1
6	9	16	3	11
7	35	35	13	22
8	0	1	0	0
9	19	17	8	7
10	2	2	2	2
11		1	0	2
12	2	2	0	1
13	0	0	0	3
14	0	2	2	1

Figure 2 provides a zoomed view of the probability plots comparing GCS 3 and 8 by age and herniation categories. It is interesting to note that a person <=40 without brain herniation but a GCS of 4 has the same probability of death as a person >40 with evidence of herniation but a GCS of 8 (see the 4th probability plot counting from the top to bottom in Figure 2).

Figure 2 Predicted probabilities for average ICP 10 to 40 mmHg



Discussion

This study evaluates different functional forms of ICP values to determine whether they are independent predictors of 28-day mortality in TBI patients managed in a neurosurgical and neurointensivist trauma center. Among several ICP measurements within the first 48 hours of sampling, the ICP averaged over the entire 48 hours remained statistically significant when all covariates were included in the model.

One of the strengths of the study is that the data comes from a completed placebo controlled randomized clinical trial with excellent follow-up for evaluation of 28-day mortality. ICP variables were based on 48 hours of ICP monitoring that occurred approximately every 20 minutes, providing over 20,000 measurements. Considering the original study was not designed to evaluate the predictive value of ICP, clinician bias is unlikely to have a substantial effect.

Another strength of the study is the excellent follow-up. Only two of the cases (0.7%) of the cases in the selected group of participants were lost to follow-up in the 28-day study period.

The patients from both the magnesium and placebo assignments were combined since the original study was unable to detect any effect. To assure that there was no effect, the categorical variable for the drug or placebo assignment was controlled for in all analyses. No statistically significant effect was detected in any of the logistic regression models. This reassurance improves the generalizabilty of this study.

Overall, the average ICP measurement over 48 hours yielded a statically significant odds ratio that remained significant with all covariates in the model. Interaction terms were evaluated but did not reach statistical significance, indicating that the effect of average ICP on mortality did not depend on the level of these variables.

One of the weaknesses of the study was the fact that ICP measurements were vulnerable to transcription errors. The ICP measurements were scopied from the monitor by the nurse and entered into the computerized medical record system. The research nurse later printed the data and transcribed the data into the study database. There were no attempts to perform double entry of ICP measurements. One possible method to validate the ICP measurements would be to take 5% or 10% randomized samples to compare with the sample descriptive statistics. Future studies on ICP monitoring may benefit from direct continuous electronic recording of ICP measurements directly into a database. Future studies should use ICP measurements taken by an electronic method for comparison to a routine clinical manner.

Although clinicians were blinded to the magnesium or placebo therapy, they were not blinded to patient enrollment in the study nor to ICP monitoring. The use of ICP monitoring as a statistically adjusted predictor and as a clinical management tool does create interactions that are difficult to reconcile. The generalizability of this study is limited to trauma centers with neurosurgeons and neurointensivists that aggressively monitor and treat elevated ICP.

The follow-up for 28-day mortality was excellent with a 0.7% loss to follow-up. Missing data from the GCS caused an additional two patients to be excluded. The measurements of ICP were taken from a computerized charting system by a trained research nurse, which should provide consistency. However, no intra-transcription analysis was performed to assure that records would be without errors. There were no assurances that transcription errors did not occur. For example, data was not typed in twice. Thus the estimates may have had wider confidence intervals due to transcription errors, which would likely have been random. The consequence of this possibility is to increase random error, so that measured associations (ORs) may be underestimated.

The probability plot provides strong insight into the relevance of the GCS. Essentially, a high GCS score indicates a mild to moderate comatose state and a more functional clinical picture. This appears to have a substantial effect on the probability of death at 28 days. Alternatively, a severe GCS rating of 3 would clinically appear to be fully comatose with absolutely no response, even to painful stimuli. This modulates the probability plot, greatly increasing the probability of death at 28 days for similar AVG ICP values. The probability plot starts at 10 since clinically, an ICP of 10 or less is considered normal and would never result in therapy to lower ICP. Measurements above 10mmHg may indicate abnormality. In this group, the mean ICP values for patients that died or survived were 14 and 18, respectively. Both group means were less than the typical 20mmHg used in clinical practice. Future studies may benefit from lowering the threshold for aggressive ICP management. Complications that may arise from aggressively lowering ICP should also be evaluated prospectively.

Conclusion

ICP averaged over the first 48 hours of monitoring is an independent predictor of 28-day mortality. We were not able to demonstrate similar significance with only 24 hours of ICP monitoring. The findings of this study are limited to TBI patients that have ICP aggressively monitored and managed to keep ICP below 20 mmHg.

These findings suggest that interventions targeting aggressive management of ICP in patients with TBI might be important to improve outcomes in this population.

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