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Mortality and long-term functional outcome associated with intracranial pressure after traumatic brain injury

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Abstract *Purpose:* Elevated intracranial pressure (ICP) has been associated with increased mortality in patients with severe traumatic brain injury (TBI). We have examined whether raised ICP is independently associated with mortality, functional status and neuropsychological functioning in adult TBI patients. *Methods:* Data from a randomized trial of 499 participants were secondarily analyzed. The primary endpoints were mortality and a composite measure of functional status and neuropsychological function (memory, speed of information processing, executive function) over a 6-month period. The area under the curve of the ICP profile (average ICP) during the first 48 h of monitoring was the main predictor of interest. Multivariable regression was used to adjust for a priori defined confounders: age, Glasgow Coma Score, Abbreviated Injury Scale–head and hypoxia. *Results:* Of the participants, 365 patients had complete 48-h ICP data. The overall 6-month mortality was 18 %. The adjusted odds ratio of mortality comparing 10-mmHg increases in average ICP was 3.12 (95 % confidence interval 1.79, 5.44; $p < 0.01$). Overall, higher average ICP was associated with decreased functional status and neuropsychological functioning ($p < 0.01$). Importantly, among survivors, increasing average ICP was not independently associated with worse performance on neuropsychological testing ($p = 0.46$). *Conclusions:* Average ICP in the first 48 h of monitoring was an independent predictor of mortality and of a composite endpoint of functional and neuropsychological outcome at the 6-month follow-up in moderate or severe TBI patients. However, there was no association between average ICP and neuropsychological functioning among survivors.

Keywords Intracranial pressure · Intracranial hypertension · Traumatic brain injury · Neuropsychological tests · Functional outcome · Critical care

Introduction

Severe traumatic brain injury (TBI) is a major cause of long-term disability and is responsible for more than one-third of deaths due to trauma in the USA [1, 2]. Elevated intracranial pressure (ICP) is associated with mortality and worse functional outcome in patients with TBI, and treatment of elevated ICP has been a central component of brain-protective strategies for many years. Accordingly, the Brain Trauma Foundation currently recommends that treatment be initiated for ICP values >20 mmHg (level II recommendation) [3].

Based on the current scientific literature, there is uncertainty whether elevated ICP plays an independent role in determining the outcome of TBI patients other than as a marker of disease severity and, consequently, whether ICP monitoring and aggressive treatment improves patient outcome. The interpretation of the current literature on intracranial hypertension is limited by the lack of detailed ICP information and the failure to account for important markers of risk, such as age, severity of injury and hypoxia and temporal changes in the management of TBI patients. Likewise, limited information is available examining the effect of raised ICP on long-term neuropsychological outcome [4–12].

The purpose of the study reported here was to investigate the role of early ICP values and patterns in predicting mortality and long-term neurobehavioral functioning in patients with severe TBI. Specifically, we examined different summarizations of ICP during the first 48 h of monitoring to test the hypothesis that ICP values or patterns are independently associated with mortality and neurobehavioral function in patients with moderate or severe TBI.

Methods

Study design

The study used prospectively collected de-identified data from a randomized trial comparing intravenous magnesium sulfate to placebo in moderate to severe TBI patients who had been admitted to Harborview Medical Center, (Seattle, WA, USA), a Level I regional trauma center, between August 1, 1998 and October 31, 2004 [13]. This study was approved by the institutional review board under waiver of informed consent.

Study population

The original trial eligibility criteria included moderate or severe TBI, age >14 years, serum creatinine level <177 μmol/L and study drug administration within the first 8 h of injury. Brain trauma was considered moderate to severe when (1) The post-resuscitation Glasgow Coma Scale (GCS) score in the emergency room was ≤12 or the GCS motor score was 1–5 in the absence of pharmacological paralysis in patients with endotracheal intubation [14] or (2) intracranial surgery was performed within 8 h of injury and defined as craniectomy, craniotomy or elevation of depressed fracture with dural repair, and did not include placement of burr or twist drill holes or intracranial pressure devices. For the purpose of our study, patients needed to have ICP monitoring placed within 12 h of injury and to have had continuous ICP monitoring maintained for the first 48 h following placement. Patients were excluded if they were pregnant, prisoners or residents abroad, aged ≤18 years or died within 48 h of admission (Fig. 1).

Measurements

The initiation and continuation of ICP monitoring were based on clinical decisions by the attending neurosurgeon and made in accordance with the Brain Trauma Foundation guidelines [15]. Therapeutic interventions were started within a maximum of 12 h from the traumatic injury to the first ICP value. Intracranial pressure measurements were recorded using an intraparenchymal pressure monitoring device, with ICP values scheduled to be collected on an

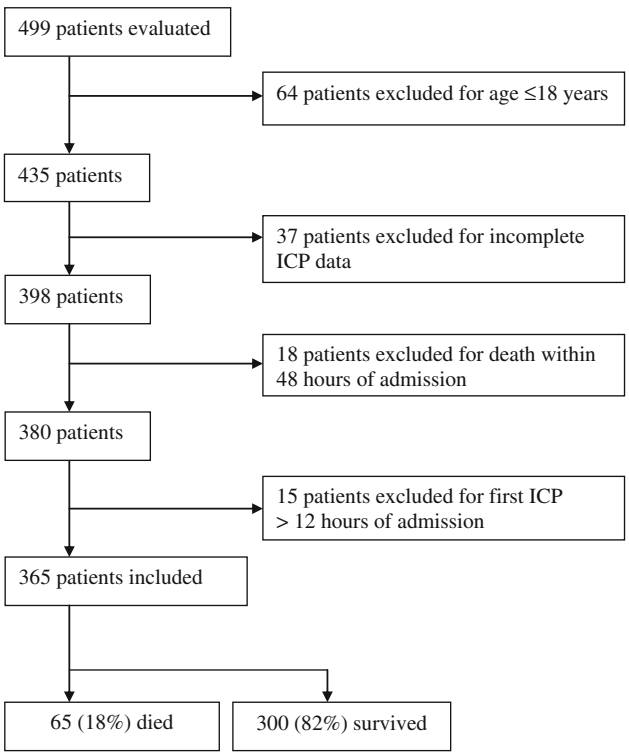

Fig. 1 Study flow chart. *ICP* Intracranial pressure

hourly basis and additional values to be included if there were any meaningful changes. Normal ICP was defined as a ICP of 0–20 mmHg. To ensure the capture of a meaningful representation of ICP values and patterns, 48-h ICP recordings were summarized using different a priori specified measures:

1. Average ICP: defined as area under the curve (AUC) of the first 48 h of ICP measurements divided by the time monitored corresponding to time-weighted ICP average.
2. Average ICP >20 mmHg: time-weighted average ICP for 48 h above the cutoff value of 20 mmHg. The length of time when values were <20 contributed 0 to the area but was counted in the time monitored. The average ICP was calculated by approximating the integral of the curve of the ICP trend line for each patient. The AUC was calculated by the trapezoid rule using the formula $0.5 \times (\text{time}_{I+1} - \text{time}_I) \times (\text{ICP}_I + \text{ICP}_{I+1})$; the AUC was then divided by the duration of monitoring. For average ICP of >20, each trapezoid measurement was made for ICP that exceeded a cutoff of 20 mmHg, with values <20 not contributing to the sum.
3. Baseline ICP: the opening ICP.
4. Maximum ICP: the highest ICP pressure recorded in 48 h
5. Last ICP: the ICP measurement at the end of the 48 h monitoring period. If ICP monitoring was stopped no longer than 3 h prior to 48 h, the last measurement available was assumed to continue up to 48 h, since discontinuation of ICP monitoring earlier than 48 h in survivors was due to patient improvement.

If there were ≥3 h of consecutive missing data and the ICP monitoring was continued, no interpolation was performed to include these gaps, reducing the sampling time to <48 h. The 3-h criterion was used to avoid incorrectly weighting the calculation of the AUC to values adjacent to these gaps. ICP measurements recorded during operative procedures were treated similarly to all other available ICP values, and the rationale was that such ICP values are indicators of valid pathophysiological effects on cerebral perfusion.

Other measurements

The baseline covariates selected for their potential clinical relevance to ICP, mortality and neurobehavioral outcome included age (continuous variable), first available arterial oxygen partial pressure (PaO_2), hypoxemia in the Emergency Department (PaO_2 <60 mmHg), GCS (continuous variable), Abbreviated Injury Scale (AIS)–head, intracranial diagnosis based on initial computed tomography findings and study treatment assignment (magnesium vs. placebo).

During the patient's stay in the Intensive Care Unit (ICU) stay, Therapeutic Intensity Level (TIL) data were collected [16]. The TIL included ICU interventions, such as sedation/paralysis, ventricular drainage, blood pressure support, aggressive hyperventilation, use of mannitol, atropine, barbiturates, calcium channel blockers and surgical decompression, from ICU admission through to the end of the first full hospital day. Each intervention was coded as occurring or not.

Study endpoints

The primary endpoints were 6-month all-cause mortality and a composite endpoint of functional [Glasgow Outcome Scale–Extended (GOS–E)] and neuropsychological outcome at the 6-month follow-up. Measures contributing to the composite endpoint are (1) Wechsler Abbreviated Scale of Intelligence (Full Scale IQ); (2) Wechsler Adult Intelligence Scale (Processing Speed Index); (3) Selective Reminding Test (sum of recall), Trails A and B; (4) Galveston Orientation and Amnesia Test and Finger Tapping (dominant and non-dominant) [13]. To calculate the composite score, we ranked the participants from 1 (worst) to n (best) on each measure separately. The ranks were converted to a percentage at or below that score and averaged over all the measures to obtain the composite score for that individual [13]. Deaths were assigned the lowest rank on all measures, and patients who were too neurologically impaired to perform the neuropsychological tests were assigned the second-lowest score.

Statistical analysis

In the bivariate analysis we compared survivors versus non-survivors, and patients with an average ICP <20 mmHg versus those with an average ICP ≥20 mmHg using the two-sample Student's t test with assumption of unequal variances (Satterthwaite's approximation of the degrees of freedom) and Fisher exact tests for two-level variables. The first 48 h of ICP monitoring was the main predictor of interest. Logistic regression was used to model mortality. A multivariate logistic regression model was fitted that included the main predictor of interest with adjustment for a priori-defined potential confounders, including age, hypoxemia, GCS, AIS–head score and treatment assignment. Multiple linear regression with robust variance estimation was used to examine the association between ICP and functional and neuropsychological function. The model included the same predictor of interest (average ICP) and a priori-selected confounders. Because measures of neuropsychological functioning only pertain to survivors, a second regression model was fitted using a composite endpoint generated without the inclusion of scores contributed by non-survivors. In this analysis, we used robust

variance estimation to account for possible mis-specification of model variation. Estimates from this model pertain to survivors only and do not require making assumptions about patients who were unable to be tested because of death. Additionally, we explored the possibility of a "cut-off value" of ICP associated with survival and poor functional outcome using ICP categories of 5-mmHg increments. An alpha level of 0.05 was considered to be statistically significant. Analyses were performed using the statistical software SPSS (ver. 17.0; SPSS, Chicago, IL) and STATA ver. 9.0 (Stata Corp, College Station, TX).

Results

A total of 365 patients, 300 (82 %) survivors and 65 (18 %) non-survivors, were eligible for inclusion (Fig. 1). The mean time between ICP measurements was 0.34 (0.09) h, giving an average of at least one ICP measurement every hour. Table 1 provides the demographics and covariates for all patients subdivided by average ICP values with a cutoff of 20 mmHg. For the entire population, the mean age was 37 ± 16 (SD) years. Variables associated with increased average ICP (cutoff of 20 mmHg) were age,

Table 1 Demographic and clinical data in patients with severe traumatic brain injury, stratified by average intracranial pressure with a cutoff of 20 mmHg

Characteristics	All patients ($n = 365$)	Average ICP <20 ($n = 306$)	Average ICP ≥20 ($n = 59$)	p value[a]
Age, mean (SD), years	37 (16)	37 (17)	34 (12)	0.05
Age >40 years, *n* (%)	130 (36)	111 (36)	19 (32)	0.66
Male, *n* (%)	280 (77)	233 (76)	47 (80)	0.62
Race/ethnicity, *n* (%)				0.81
Caucasian	286 (78)	240 (78)	46 (78)	
African-American	14 (4)	13 (4)	1 (2)	
Native American	8 (2)	7 (2)	1 (2)	
Asian/Pacific Islander	32 (9)	25 (8)	7 (12)	
Hispanic	25 (7)	21 (7)	4 (7)	
Admission hypoxemia, *n* (%)	96 (26)	81 (27)	15 (25)	1.00
PaO_2, mean (SD), mmHg[b]	48 (12)	48 (12)	48 (13)	0.90
AIS-head, mean (SD)	4.6 (0.6)	4.6 (0.6)	4.7 (0.5)	0.03
ISS, mean (SD)	31 (10)	30 (10)	33 (11)	0.10
ISS non-head, mean (SD)	10 (10)	10 (10)	12 (11)	0.38
Both pupils fixed and dilated, *n* (%)	3 (0.8)	3 (1)	0 (0)	1.00
Intracranial diagnosis, *n* (%)				
Intracerebral hematoma	45 (12)	34 (11)	11 (19)	0.13
Epidural hematoma	76 (21)	56 (19)	18 (31)	0.05
Subdural hematoma	203 (56)	168 (55)	35 (59)	0.57
Subarachnoid hemorrhage	236 (65)	198 (65)	38 (64)	1.00
Intraventricular hemorrhage	114 (31)	100 (33)	14 (24)	0.22
Diffuse axonal injury	133 (36)	112 (37)	21 (36)	1.00
Cerebral edema[c]	226 (62)	183 (60)	43 (73)	0.08
Herniation[d]	43 (12)	35 (11)	8 (14)	0.66
Brain stem injury	18 (5)	14 (5)	4 (7)	0.51
Skull fracture, *n* (%)	189 (52)	151 (49)	38 (64)	0.05
Emergency room GCS, median (IQR)	7 (5–9)	4 (7–9)	6 (7–9)	0.94
Emergency room GCS, *n* (%)				0.82
3–5	83 (25)	72 (26)	11 (22)	
6–8	127 (39)	106 (38)	21 (42)	
9–15	120 (36)	102 (36)	18 (36)	
Lowest GCS in first 24 h, median (IQR)	7 (4–7)	7 (4–7)	6 (3–7)	0.02
Lowest GCS in first 24 h ≤8, *n* (%)	279 (78)	231 (77)	48 (84)	0.30
Treatment assignment: magnesium (n1), placebo (n2) group	187, 178	154, 152	33, 26	0.48

ICP Intracranial pressure, *AIS* Abbreviated Injury Score, *ISS* Injury Severity Score (sum of squares of top three regions, both including and excluding head), *GCS* Glasgow Coma Scale, *n* number of patients, *SD* standard deviation, *IQR* interquartile range

[a] p values from two-sided Student's t test with no assumption of equal variance for continuous variables and two-sided Fisher Exact test for categorical variables

[b] Hypoxemia is defined as an arterial oxygen partial pressure (PaO_2) <60 mmHg; only the hypoxic values are represented

[c] Edema is defined as mild to severe brain swelling based on the following 1998 AIS manual codes: 140660.3, 40662.3, 140664.4, 140666.5, 140668.3, 140670.3, 140672.4, 140674.5

[d] Herniation is defined as severe brain swelling with absent ventricles or brainstem cisterns (1998 AIS manual codes: 140666.5, 140674.5)

Table 2 Intracranial pressure and cerebral perfusion pressure characteristics during the first 48 h of ICP monitoring based on average ICP

Characteristics	All patients ($n = 365$)	Average ICP <20 ($n = 306$)	Average ICP ≥20 ($n = 59$)	p value[a]
Baseline values[b]				
ICP, mean (SD), mmHg	18 (13)	16 (10)	30 (17)	<0.01
MAP, mean (SD), mmHg	124 (16)	123 (16)	128 (16)	0.04
CPP, mean (SD), mmHg	105 (19)	107 (19)	98 (22)	<0.01
MAP <60, *n* (%)	23 (6)	17 (6)	6 (10)	0.24
Systolic BP < 90, *n* (%)	95 (26)	75 (25)	20 (34)	0.15
48-hour ICP patterns, mean (SD), mmHg				
Average ICP (by AUC)	15 (7)	13 (4)	25 (8)	<0.01
Average ICP above 20 (by AUC)	1.4 (3.8)	0.5 (0.8)	6.0 (7.9)	<0.01[c]
Maximum ICP	33 (18)	30 (15)	51 (23)	<0.01
Last ICP	15 (8)	13 (7)	24 (9)	<0.01
48-hour average CPP, mean (SD), mmHg	77 (10)	78 (9)	68 (10)	<0.01
ICU intervention variables, *n* (%)				
Sedation/paralysis	365 (100)	304 (100)	61 (100)	–
Ventricular drainage	14 (4)	9 (3)	5 (9)	0.06
Mannitol	231 (63)	179 (59)	52 (88)	<0.01
Blood pressure support	87 (24)	62 (20)	25 (42)	<0.01
Atropine	12 (3)	7 (2)	5 (8)	0.03
Aggressive hyperventilation[d]	338 (93)	285 (93)	53 (90)	0.41
Barbiturates	1 (0.3)	1 (0.3)	0 (0)	1.00
Surgical decompression	118 (32)	99 (32)	19 (32)	1.00
Calcium channel blockers	3 (1)	3 (1)	0 (0)	1.00
Total TIL score, mean (SD)	3.2 (1.1)	3.1 (1.1)	3.7 (1.0)	<0.01
Total TIL score, median (IQR)	3 (2–4)	3 (2–4)	4 (3–4)	<0.01
Anticonvulsants	362 (99)	303 (99)	59 (100)	1.00

ICP Intracranial pressure, *MAP* Mean arterial pressure, *CPP* cerebral perfusion pressure, *AUC* area under the curve, *TIL* therapeutic intensity level (number of different interventions from ICU (Intensive Care Unit) admission through the end of full first hospital day, range 0–9 and excluding anticonvulsants

[a] p values from two-sided Student's t test with no assumption of equal variance for continuous variables, and two-sided Fisher Exact test for categorical variables

[b] Baseline ICP is the first recorded value; baseline MAP is the average over the first 3 hours of recording; baseline CPP is the difference between baseline MAP and baseline ICP

[c] p value from Mann–Whitney for average ICP above 20 mmHg

[d] Defined as $PaCO_2$ <30 mmHg, whether there was deliberate hyperventilation or not

AIS-head, epidural hematoma, skull fracture, and lowest GCS (Table 1). Table 2 shows the ICU physiologic variables and interventions by average ICP.

Mortality

Non-survivors were older, scored worse on injury severity measures (AIS–head, GCS), were more likely to have fixed and dilated pupils and to experience hypoxemia. An intracranial diagnosis of herniation, edema and intraventricular hemorrhage (IVH) was more frequent among non-survivors (data not shown). Baseline values during the first 3 h of monitoring, ICP patterns and ICU interventions are summarized in Table 3. Average ICP, average ICP >20, and baseline, maximum and last ICP were significantly higher among non-survivors than among survivors. Initial and 48-h average cerebral perfusion pressure (CPP) was lower among non-survivors.

During the ICU stay, there were significantly more interventions, as indicated by a higher total TIL score among non-survivors compared with survivors. Non-survivors were more likely to have ventricular drainage and surgical decompression and to receive mannitol and blood pressure support.

The unadjusted odds ratio (OR) of death for increasing average ICP was 2.33 [95 % confidence interval (CI) 1.49, 3.62; $p < 0.01$] per 10-mmHg higher average ICP. After accounting for confounders (age, hypoxemia, GCS, AIS–head score and treatment assignment), the adjusted OR for mortality was 3.12 (95 % CI 1.79, 5.44; $p < 0.01$). The findings were not substantially different using average ICP >20 or other ICP patterns.

Neuropsychological endpoints

Table 4 summarizes the neuropsychological performance scores and functional status data collected at 1, 3 and 6 months after injury, classified by an average ICP cut-off of 20 mmHg for the entire population and for survivors. At 6 months, there were significant differences between patients with high versus low average ICP in GOS-E, overall intellectual functions (Wechsler Abbreviated

Table 3 Intracranial pressure and cerebral perfusion pressure characteristics during the first 48 h of ICP monitoring based on survival status

Characteristics	All patients ($n = 365$)	Survivors ($n = 300$)	Non-survivors ($n = 65$)	p value[a]
Baseline values[b]				
ICP, mean (SD), mmHg	18 (13)	17 (12)	23 (16)	0.02
MAP, mean (SD), mmHg	124 (16)	125 (15)	121 (19)	0.14
CPP, mean (SD), mmHg	105 (19)	107 (18)	98 (24)	<0.01
MAP <60, *n* (%)	23 (6)	17 (6)	6 (9)	0.27
Systolic BP <90, *n* (%)	95 (26)	75 (25)	20 (31)	0.35
48-hour ICP patterns, mean (SD), mmHg				
Average ICP (by AUC)[c]	15 (7)	14 (6)	18 (9)	<0.01
Average ICP above 20 (by AUC)[d]	1.4 (3.8)	1.0 (2.5)	3.0 (7.1)	<0.01[g]
Maximum ICP	33 (18)	32 (16)	40 (24)	<0.01
Last ICP	15 (8)	14 (8)	17 (11)	0.04
48-hour average CPP, mean (SD), mmHg[e]	77 (10)	77 (10)	74 (12)	0.06
ICU intervention variables, *n* (%)				
Sedation/paralysis	365 (100)	300 (100)	65 (100)	–
Ventricular drainage	14 (4)	7 (2)	7 (11)	<0.01
Mannitol	231 (63)	180 (60)	51 (79)	<0.01
Blood pressure support	87 (24)	56 (19)	31 (48)	<0.01
Atropine	12 (3)	11 (4)	1 (2)	0.70
Aggressive hyperventilation[f]	338 (93)	278 (93)	60 (92)	1.00
Barbiturates	1 (0.3)	0 (0)	1 (2)	0.18
Surgical decompression	118 (32)	87 (29)	31 (48)	<0.01
Calcium channel blockers	3 (1)	2 (1)	1 (2)	0.45
Total TIL score, mean (SD)	3.2 (1.1)	3.1 (1.0)	3.8 (1.0)	<0.01
Total TIL score, median (IQR)	3 (2–4)	3 (2–4)	4 (4–5)	<0.01
Anticonvulsants	362 (99)	298 (99)	64 (99)	0.45

ICP intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *n* number of patients, *BP* Blood pressure

[a] p values from two-sided Student's t test with no assumption of equal variance for continuous variables, and two-sided Fisher Exact test for categorical variables

[b] Baseline ICP is the first recorded value; baseline MAP is the average over the first 3 h of recording; baseline CPP is the difference between baseline MAP and baseline ICP

[c] For the average ICP over 48 h the values ranged from 6 to 24, with a median of 15 and IQR of (11, 18)

[d] Area under the curve for elevated ICP over cut-off criteria of 20 mmHg monitored for 48 h

[e] For the average CPP over 48 h the values ranged from 62 to 93, with a median of 76 and IQR of (70, 83)

[f] Defined as $PaCO_2$ <30 mmHg, whether there was deliberate hyperventilation or not

[g] p value from Mann–Whitney for average ICP >20

Scale of Intelligence–Full Scale IQ), information processing speed (Wechsler Adult Intelligence Scale–Processing Speed Index), episodic memory and learning (Selective Reminding), executive functions (Trails B) and various activities of everyday life (Functional Status Examination).

The unadjusted difference in the composite score based on mortality, functional status and neuropsychological measures for a 10-mmHg increase in average ICP was −9.0 (95 % CI −13.4, −4.7). After accounting for confounders, the adjusted difference in the composite score for each 10-mmHg increment in average ICP was −8.2 (95 % CI −12.0, −4.3; $p < 0.01$; Table 5), indicating worse scores among patients experiencing higher ICP in the first 48 h of monitoring. The analysis of ICP cut-off suggested that for ICP ≥25 mmHg, survival seemed to be significantly lower (Fig. 2).

When we recomputed the composite score restricting the analysis to survivors ($n = 300$), there was no significant difference in overall functional and neuropsychological performance with higher average ICP (adjusted difference in mean score for each 10-mmHg increase in ICP −1.6, 95 % CI −5.7, 2.6; $p = 0.46$).

Discussion

In our study, we examined ICP summary variables to determine whether the ICP values and patterns in moderate or severe TBI patients were independent predictors of mortality and neurobehavioral function. Average ICP during the first 48 h of monitoring was an independent predictor of mortality at the 6-month follow-up and as good as other ICP patterns in predicting 6-month mortality. Elevated ICP was associated with worse functional outcome and neuropsychological performance in the whole study population. Importantly, when focusing on survivors, we found that there was no association between ICP and neurobehavioral functioning at the 6-month

Table 4 Median scores for functional status and neuropsychological tests administered at 1, 3 and 6 months after injury, where deceased and CNS-untestable subjects are ranked as worst and 2nd-worst respectively

Outcome measures	Entire sample			Survivors only		
	Average ICP <20	Average ICP ≥20[a]	*p* value[b]	Average ICP <20	Average ICP ≥20[a]	*p* value[b]
1-month follow-up						
Subjects, *N*	296	58		250	39	
Deaths, *n* (%)	42 (14)	17 (29)		–	–	
GOAT[c], median	67	Untestable	0.25	85	94	0.25
GOS-E[d], median	3	3	<0.01	3	3	0.29
3-month follow-up						
Subjects, *N*	283	49		237	30	
Deaths, *n* (%)	45 (16)	17 (35)		–	–	
GOAT, median	90	72	0.07	95	95	0.60
GOS-E, median	4	3	0.01	5	5	0.70
FSE[e], median	22	26	0.01	20	19.5	0.96
6-month follow-up						
Subjects, *N*	287	54		241	35	
Deaths, *n* (%)	46 (16)	19 (35)		–	–	
WASI (FSIQ)[f], median	86	58	0.01	92.5	94	0.79
WAIS (PSI)[g], median	76	Untestable	0.02	81	83.5	0.67
SRT (sum of recall)[h], median	64	Untestable	0.01	71	69	0.72
Trails A (time)[i], median	46	101	0.08	38	28	0.15
Trails B (time)[i], median	122	265	0.04	94.5	75	0.46
Finger tapping (dominant hand)[j], median	41	Untestable	0.06	45	49.5	0.22
Finger tapping (non-dom. hand)[j], median	37	Untestable	0.05	42	45	0.33
GOAT, median	91	82.5	0.04	95	95	0.58
GOS-E, median	5	3	0.03	5	5	0.98
FSE, median	19	27	0.01	16	16.5	0.60
Outcome composite (average percentile)[k]	58	38	0.03	63	65	0.55

[a] Deceased subjects are ranked as the worst outcome for each measure; subjects untestable due to central nervous system (CNS) issues are ranked second-worst. (The median score for some measures was a subject that was untestable)

[b] *p* value from two-sided Wilcoxon Rank-Sum test

[c] Galveston Orientation and Amnesia Test

[d] Glasgow Outcome Scale–Extended

[e] Functional Status Examination—a measure that evaluates change in various activities of everyday life as a function of injury or health condition

[f] Wechsler Abbreviated Scale of Intelligence (Full Scale IQ)—an index of overall intellectual functions

[g] Wechsler Adult Intelligence Scale (Processing Speed Index) 3rd Edition—an estimate of information processing speed

[h] Selective Reminding Test—a measure of episodic memory and learning

[i] Trails A and B—a measure of attention and executive functions

[j] Finger Tapping Test—a measure of motor speed with the dominant and non-dominant hand

[k] A rank-based average of all 15 measures, interpreted as the average percentile within the sample (0–100), and for which a higher value indicates a better outcome

follow-up. This is the first report describing with accuracy the relationship between ICP and performance and observing a lack of effect of ICP on functioning among survivors, who are in fact the individuals for whom performance really matters.

Our primary outcome was a comprehensive composite score known to be sensitive to the integrity of the brain. The results of several published studies indicate that pathophysiological events, including elevated ICP, can have some effects on neuropsychological outcome [6, 17–19]. The findings of our study suggest that raised average ICP during the first 48 h of admission does not necessarily have independent adverse effects on the neuropsychological and functional abilities of TBI survivors, as the association of ICP and outcome was mostly contributed by the excess mortality. Excluding deaths could introduce bias due to an inability to adhere to an intention-to-treat approach. However, our focus was to describe the relationship between ICP and functioning; therefore, the inference regarding survivors is equally important. The lack of association between neuropsychological function and early ICP values among survivors has potential implications for treatment. It is reassuring to observe that patients with different ICP profiles in the ICU can function in comparable ways at 6 months post-injury, provided they survive to achieve this milestone.

Previous studies reported strong associations between ICP values or patterns and mortality, with a several fold

Table 5 Multivariate regression with robust variance estimation predicting the composite neuropsychological and functional outcome among all patients

Covariate	Entire sample		Survivors only	
	Estimate (95 % CI)	*p* value	Estimate (95 % CI)	*p* value
Average ICP, 10-mmHg difference	−8.3 (−12.0, −4.6)	<0.01	−1.2 (−5.4, 2.9)	0.56
Age, 10-year difference	−5.2 (−6.7, −3.6)	<0.01	−2.9 (−4.4, −1.4)	<0.01
Hypoxia, vs. no hypoxia[a]	−3.6 (−9.0, −1.8)	0.19	−2.2 (−7.0, 2.6)	0.36
Glasgow Coma Scale[b]		<0.01		<0.01
Score 6–8 (vs. 3–5)	18.4 (12.3, 24.5)		8.7 (2.7, 14.6)	
Score 9–14 (vs. 3–5)	30.1 (23.6, 36.5)		18.2 (12.1, 24.4)	
AIS–head, 1-point difference[c]	−8.8 (−13.2, −4.5)	<0.01	−5.7 (−9.3, −2.0)	<0.01
$MgSO_4$ treatment group, vs. placebo	3.0 (−2.0, 8.0)	0.23	1.2 (−3.2, 5.5)	0.59

Estimates reflect the difference in the composite outcome associated with a given characteristic relative to the reference group, adjusted for all other covariates in the model. The composite outcome is a rank-based average of 15 neuropsychological and functional outcome measures collected at 1, 3 and 6 months post-injury. This composite is expressed as a percentile of the sample (0–100), with a higher percentile indicating a better outcome

ICP intracranial pressure, *AIS* Abbreviated Injury Score, *CI* confidence interval, *$MgSO_4$* magnesium sulfate

[a] Hypoxia was defined as PaO_2 <60 mmHg

[b] Emergency Room Glasgow Coma Scale modeled as categorical variable

[c] AIS can range from 1 (minor injury) to 6 (unsurvivable), with scores in this sample ranging from 3 to 5 treated as continuous

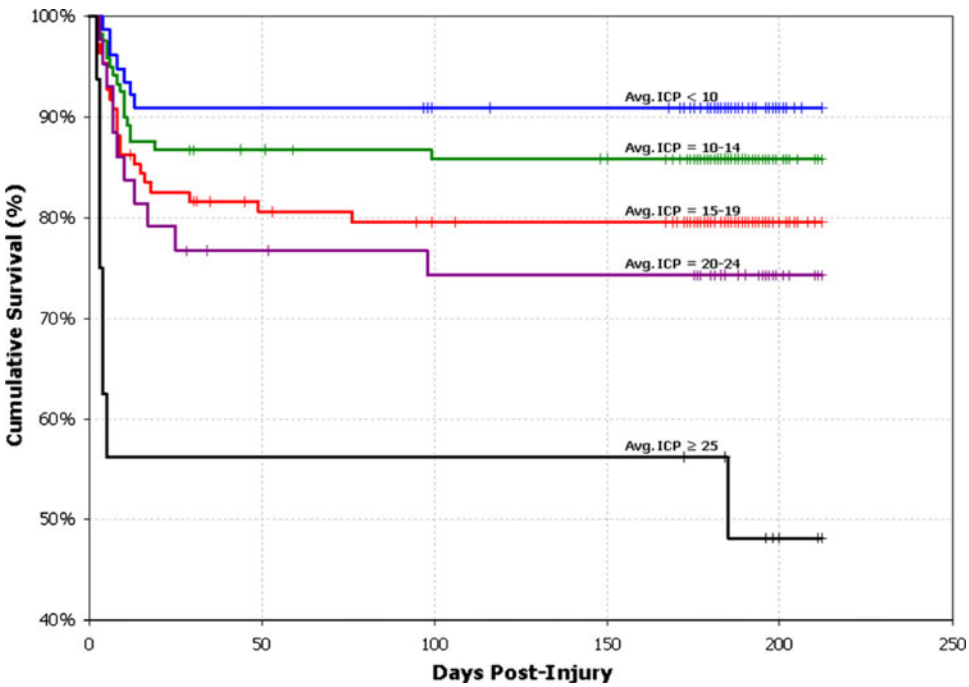

Fig. 2 Kaplan–Meier survival curves stratified by categories of average ICP in the first 48 h of monitoring

increase in mortality associated with ICP abnormalities, particularly for ICP values >40 mmHg and refractory ICP patterns [20]. Our study is consistent with the association between elevated ICP and mortality; however, among the patients included in our study, the strength of the association appeared to be weaker than previously reported. It is possible that our study differs from previous ones in that the average ICP was not exceedingly elevated. In addition, the failure to accurately account for confounding in previous studies might explain the exaggerated relationship found in those studies. Other studies have found that TBI patients with ICP >20 or >40 mmHg have worse mortality and neurological outcomes based on the GOS [4, 21–24]. Our study differs because we report a much lower mortality (18 %) than these previous studies. This finding may be explained by the fact that our study population includes moderate TBI patients.

According to a systematic review [20], no randomized trials have been published investigating the effect of ICP

monitoring-guided treatment on mortality or neurobehavioral function. Of note, a multicenter, randomized controlled trial comparing ICP-guided therapy versus therapy using an empiric protocol in severe TBI patients is currently underway in South America (ClinicalTrials.gov Identifier: NCT01068522).

One of the strengths of our study is the high follow-up rate and the high quality of the data collected as part of a placebo-controlled randomized clinical trial. ICP variables were based on 48 h of ICP monitoring that occurred approximately every 20 min, providing over 23,000 measurements. Considering the original study was not designed to evaluate the predictive value of ICP, clinician bias is unlikely to have a substantial effect.

This study has several limitations. First, ICP measurements were recorded from the monitor by a nurse, entered into the computerized medical record system and then transcribed into the study database. Therefore, ICP measurements were vulnerable to transcription errors and less reliable than automated data capture [25]. Future studies on ICP monitoring may benefit from direct continuous electronic recording of ICP measurements. Second, although clinicians were blinded to the treatment subjects received (magnesium or placebo therapy), they were not blinded to patient enrollment in the study or to ICP monitoring. Outcome examiners were blinded to both study intervention and ICP. Third, the use of ICP values as a statistically independent predictor needs to be interpreted with caution outside the context of a randomized trial of ICP management. In the study setting, all patients had ICP monitoring and were aggressively treated for elevated ICP >20 mmHg. Intracranial hypertension can therefore represent a marker of brain trauma severity rather than a modifiable risk factor to improve mortality. The relative value of ICP as a marker of disease versus a treatable entity remains therefore unclear, and the interpretation of ICP as independent predictor should consequently be viewed in the context of the 48-h monitoring window and account for the clinical course and interventions occurring during the monitoring time.

In our study population, the average ICP was 15 mmHg, which is less than the typical 20 mmHg threshold for treating ICP in clinical practice. Although the non-surviving group had a significantly greater average ICP, associated with a higher TIL for the first 48 h, the lower mean and last ICP values would suggest that both groups were "treatment responders," i.e. had a non-refractory ICP pattern on average. Thus, mortality might not be entirely attributable to refractory intracranial hypertension and could also be related to the more aggressive treatment needed to control ICP in the non-survivors group. In order to further understand this relationship between the definition of intracranial hypertension and the consequences of treatment, future studies may consider varying the threshold for aggressive ICP management. Complications that may arise from aggressively lowering ICP should also be prospectively evaluated.

Finally, in this study that makes secondary use of data from a randomized trial, one cannot be sure all confounders were identified and controlled.

Conclusion

In the current study, ICP averaged over the first 48 h of monitoring was an independent predictor of mortality. Raised ICP was associated with worse outcome in the study population as a whole, but there was no association between average ICP and functional and neuropsychological outcome at the 6 month follow-up among survivors. These data suggest that survivors of severe TBI might function at similar levels irrespective of their ICP characteristics in the ICU. The reasons for the different effects of ICP on mortality and the functional outcome of survivors are not clear. Nonetheless, these findings can have implications in clinical decision-making and prognostic considerations among TBI survivors.

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