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Responsiveness to therapy for increased intracranial pressure in traumatic brain injury is associated with neurological outcome

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ABSTRACT

In patients with severe traumatic brain injury, increased intracranial pressure (ICP) is associated with poor functional outcome or death. Hypertonic saline (HTS) is a hyperosmolar therapy commonly used to treat increased ICP; this study aimed to measure initial patient response to HTS and look for association with patient outcome.

Patients >17 years old, admitted and requiring ICP monitoring between 2008 and 2010 at a large urban tertiary care facility were retrospectively enrolled. The first dose of hypertonic saline administered after admission for ICP >19 mmHg was recorded and correlated with vital signs recorded at the bedside. The absolute and relative change in ICP at 1 and 2 h after HTS administration was calculated. Patients were stratified by mortality and long-term (≥6 months) functional neurological outcome.

We identified 46 patients who received at least 1 dose of HTS for ICP > 19, of whom 80% were male, mean age 34.4, with a median post-resuscitation GCS score of 6. All patients showed a significant decrease in ICP 1 h after HTS administration. Two hours post-administration, survivors showed a further decrease in ICP (43% reduction from baseline), while ICP began to rebound in non-survivors (17% reduction from baseline). When patients were stratified for long-term neurological outcome, results were similar, with a significant difference in groups by 2 h after HTS administration.

In patients treated with HTS for intracranial hypertension, those who survived or had good neurological outcome, when compared to those who died or had poor outcomes, showed a significantly larger sustained decrease in ICP 2 h after administration. This suggests that even early in a patient's treatment, treatment responsiveness is associated with mortality or poor functional outcome. While this work is preliminary, it suggests that early failure to obtain a sustainable response to hyperosmolar therapy may warrant greater treatment intensity or therapy escalation.

Introduction

Traumatic brain injury (TBI) is the leading cause of death after injury [1], with incidence peaks in children, adolescents, and adults over the age of 65 [2]. One study estimated the economic impact of TBI at $9.2 billion in lifetime medical costs and $51.2 billion in lost productivity [3].

Management of severe TBI focuses on preventing and treating secondary insults caused by hypoxia, hypotension, and intracranial hypertension (ICH). Treatment for severe TBI is algorithmic [4] and directed at maintenance of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) within ranges that do not further exacerbate secondary injury such as oedema, inflammation, and ischaemia. Hyperosmolar therapy, traditionally with mannitol, has been commonly accepted as an acute treatment of cerebral oedema for decades. More recently, hypertonic saline (HTS) has become popular [5–7]. While there is as yet no definitive evidence to support one agent as clearly superior, one meta-analysis suggests that equi-osmolar HTS may be more effective than mannitol [8]. At our institution, HTS is regularly used as the first-line hyperosmolar therapy as part of a larger tiered protocol.

Accurate prediction of outcome after severe TBI has proved difficult. The large International Mission for Prognosis and Clinical Trial design in TBI (IMPACT) study found various admission characteristics such as patient demographics, Glasgow Coma Score

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(GCS), presence of secondary insults or structural abnormalities on imaging, and laboratory abnormalities to be predictive of eventual outcome [9]. However, clinical course after TBI is often unpredictable, and most prognostic models are unable to incorporate information gleaned from the patients' treatment and recovery. In this study, we sought to evaluate the actual effect of early ICP-directed treatment on prognosis following severe TBI.

Materials and methods

Patients

Study subjects were admitted to the R Adams Cowley Shock Trauma Center, a level I tertiary medical center, between 2008 and 2010. With approval from the Institutional Review Board (IRB), data were collected retrospectively on patients older than 17 years of age admitted to the Neurotrauma Critical Care Unit (NTCCU) with severe TBI who required invasive ICP monitoring. Severe TBI was defined as post-resuscitation GCS < 9 and TBI confirmed by computed tomography (CT). Patients were then included if they received at least one dose of hypertonic saline for the reduction of intracranial pressure during the duration of ICP monitoring.

Data collection

Patient demographics, mechanism of injury, routine vital signs, method of ICP monitoring, and need for surgical intervention with cranial decompression were recorded. Admission head CT was assigned a Marshall Classification score [10] according the presence of basal cistern compression, midline shift >5 mm, and lesions $>25\ cm^3$. Outcomes measured included in-hospital mortality (on discharge from the Shock Trauma Center) and long-term functional outcome as measured by the extended Glasgow Outcome Scale (GOSE) [11], evaluated at least 6 months after discharge. Neurological outcomes were divided into 'poor neurological outcome' (GOSE 1–4 at least 6 months after discharge or in-hospital mortality) or 'good neurological outcome' (GOSE 5–8).

Routine vital signs including ICP, cerebral perfusion pressure (CPP), and mean arterial pressure (MAP) were recorded from manually documented bedside records. When ICP > 19, values were recorded every 15 min; otherwise, hourly measurements are used. The timing of the first dose of HTS administration was correlated with recorded vital signs data and only included for analysis if ICP in the hour of administration was >19 to exclude instances of HTS administration for purposes other than amelioration of ICH.

Management protocol

Patients with severe TBI admitted to the R Adams Cowley Shock Trauma Center are admitted to a dedicated NTCCU and managed according to a standardized tiered protocol in accordance with the Brain Trauma Foundation Guidelines [Brain Trauma Foundation 2007]. Treatment targets the maintenance of ICP < 20 mmHg and CPP > 60 mmHg, as previously described elsewhere [12]. All patients included in the study had placement of a clinically indicated intraparenchymal monitor (Camino®; Integra NeuroSciences) or intraventricular catheter (Codman; Raynham, MA).

Only the first administration of a bolus dose of HTS was included for each patient to avoid confounding effect of multiple treatments. Patients received a bolus dose of 3% NaCl solution with a volume of either 250 ml or 500 ml, at the clinician's discretion.

Statistical analysis

Statistical analyses were performed in Excel (Microsoft; Redmond, WA), SAS (Cary, NC) and Matlab Student v7.10 (Natick, MA). Demographic data were summarized as percentages or means with standard deviation or error and medians with interquartile range. Ninety-five percent confidence intervals are reported. The Student's *t*-test was used to compare means and non-parametric tests were used to compare medians. Probability values for results being due to chance (p) of 0.05 or less were considered statistically significant. p-Values of more than one decimal place below 0.01 are shown as <0.001.

Results

Inclusion criteria were met by 46 subjects. Subjects were primarily male (80%), mean age 34.4 ± 4.0 with a median post-resuscitation GCS score of 6, IQR 6–7 and a median Marshall CT score of 2.5, IQR 2–3 (Table 1). Median Injury Severity Score was 29, IQR 25–37.5. 95.7% of patients suffered blunt injury; 45.7% had multiple severe injuries. In-hospital mortality was 19.6%. The median length of stay (LOS) was 15.3 days (IQR 11.9–21.8), with a median Intensive Care Unit (ICU) stay of 13.2 days (IQR 10.8–18.6). Craniectomy or craniotomy for ICP control was required by 45.6% of patients. Patients received either 250 ml or 500 ml 3% NaCl solution. 500 ml was administered to 5/9 patients who went on to die in-hospital, 18/37 patients who survived, 9/17 patients who had poor long-term outcome, and 11/26 with good long-term outcome.

In all patients, after the first dose of HTS for ICH, ICP was 7.1 ± 7.4 mmHg lower after 1 h and 8.7 ± 7.3 mmHg lower after 2 h ($p < 0.05$), a relative decrease of 30% and 38%, respectively (Table 2).

Table 1
Patient and injury characteristics.

	All ($n=46$)	Alive at discharge ($n=37$)	In-hospital death ($n=9$)	p	Good outcome* ($n=26$)	Poor outcome** ($n=17$)	p
Age (y), mean ± SD	34.4 ± 13.8	33.4 ± 13.0	38.4 ± 16.9	ns	30.3	37.2	ns
Males, n (%)	37 (80.4)	31 (83.8)	6 (66.7)	ns	84.6	70.6	ns
GCS, post-resuscitation, median (IQR)	6 (6–7)	6 (6–7)	6 (3–6)	<0.05	6 (4–6)	6 (6–7)	ns
Marshall CT score, median (IQR)	2.5 (2–3)	2 (2–3)	3 (2–3)	ns	2.5	2.7	ns
Blunt injury, n (%)	44 (95.7)	35 (94.6)	9 (100)	ns	26 (100)	15 (88.2)	ns
ISS, median (IQR)	29 (25–37.5)	26 (21–36)	34 (29–43)	ns	26 (21–37.5)	29 (26–43)	ns
Polytrauma, n (%)***	21 (45.7)	15 (40.1)	6 (66.7)	ns	11 (42.3)	9 (52.9)	ns
LOS (days), median (IQR)	15.3 (11.9–21.8)	17.6 (13.1–22.9)	6.5 (5.1–7.2)	<0.001	16.6 (12.9–22.0)	11.8 (6.5–17.4)	ns
ICULOS (days), median (IQR)	13.2 (10.8–18.6)	14.6 (11.6–19.3)	6.2 (4.6–6.8)	<0.01	13.9 (11.7–18.7)	10.6 (6.4–15.2)	ns
Craniotomy/craniectomy, n (%)	21 (45.6)	19 (51.4)	2 (22.2)	ns	26 (46.2)	8 (47.1)	ns

GCS, Glasgow Coma Scale; CT, computed tomography; ISS, Injury Severity Score; LOS, Length of stay; ICU, intensive care unit; ns, not statistically significant.
* 6-month GOSE 5–8.
** 6-month GOSE 1–4 or in-hospital death.
*** Defined as non-head ISS > 15.

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Table 2
Effect of the first dose of hypertonic saline on physiologic variables.

Parameter	1 h before	At administration	1 h after	2 h after
ICP	19.7	21.5	14.4*	12.8*
MAP	85.9	86.9	85.4	82.2
CPP	66.9	65.3	69.3	70.7

* $p < 0.05$ when compared to value at time of HTS administration.

CPP trended upwards at each time point, while MAP remained relatively stable.

Patients were stratified first by in-hospital mortality (Table 3). All patients showed a significant decrease in ICP 1 h after HTS administration, with no significant difference between the 2 groups. Two hours after HTS administration, however, survivors showed a further decrease in ICP, while ICP began to rebound in non-survivors (Fig. 1; $p < 0.05$ at 2 h post administration). Absolute ICP decrease from baseline at 2 h post-administration was 2.4 times greater in survivors than in those who died during hospitalization. The relative decrease in ICP after 1 h was 32% in survivors versus 23% in non-survivors (not significant). At 2 h after HTS administration, the relative ICP decrease from baseline was 43% in survivors and 17% in non-survivors ($p < 0.05$) (Fig. 2).

Patients were also dichotomized into 'good' or 'poor' long-term neurological functional outcome (Table 4). Again, both patient groups showed a significant decrease in ICP 1 h after HTS administration (no difference between groups). At 2 h after HTS administration, patients with a good long-term outcome showed a significantly better ICP decrease (10.8 ± 8.1 mmHg versus 6.2 ± 5.1 mmHg in patients with poor outcome), or a relative decrease from baseline of 46.8% versus 26.8%. ICP improvement in those with good neurological outcome was 1.7 times greater 2 h after HTS administration than in those with poor outcome ($p < 0.05$).

Discussion

Current medical therapy cannot ameliorate the primary injury in TBI, so management focuses on minimizing secondary insults, mainly ICH and cerebral hypoperfusion, which are known to be associated with death and poor neurological outcomes [13–16]. Once adequate sedation and analgesia are obtained, hyperosmolar therapy is usually the first-line treatment for acute treatment of ICH. Our data suggest that there is a significant correlation between ICP control after HTS administration and patient mortality and functional outcome; further, this association exists even when looking at only the first dose of HTS used for increased intracranial pressure. While CPP trended favourably after HTS administration, changes did not reach significance presumably because of the proportionally smaller changes from baseline values.

Other groups have shown a clear dose-response relationship between hyperosmolar therapy and ICP [17–20]. Our group has shown that brief episodes of ICH [21] and the absolute 'dose' of elevated ICP [22] are associated with mortality and poor neurological outcome after TBI. At our institution, HTS is a first-tier treatment for ICH. The ability to anticipate patients with poor intracranial compliance allows for more rapid treatment escalation, aggressive management, and earlier preparation for surgery if indicated. The likelihood that patients with ICH refractory to repeated treatment will fare poorly seems obvious, however, to the best of our knowledge this study is the first to show that

Table 3
Effect of the first dose of hypertonic saline on physiologic variables by patient survival to discharge.

Parameter	Alive				Dead			
	1 h before	At administration	1 h after	2 h after	1 h before	At administration	1 h after	2 h after
ICP	19.7	21.6	13.9*	11.8*	19.7	21.3	16.3*	17.3**
MAP	85.2	86.8	84.8	82.2	89.3	87.5	87.9	81.8
CPP	67.1	65.6	69.3	71.7	65.8	63.7	68.7	66.1

* $p < 0.05$ when compared to value at time of HTS administration.
** $p < 0.05$ when compared to 'alive' group at same time point.

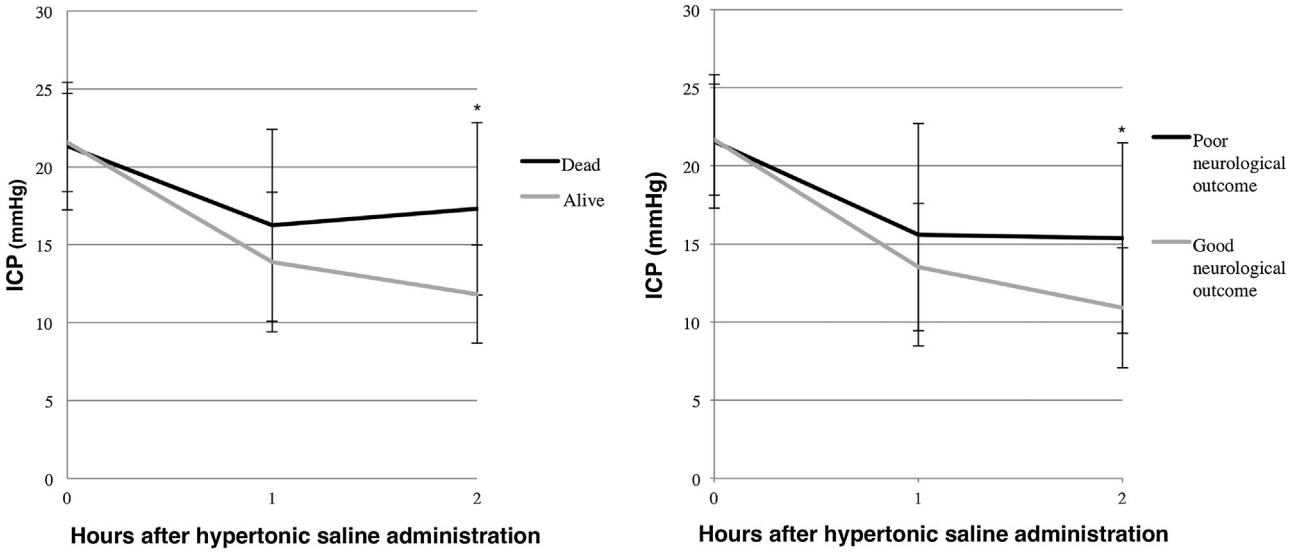

Fig. 1. Intracranial pressure after administration of first dose of hypertonic saline for intracranial hypertension. *$p < 0.05$ between groups.

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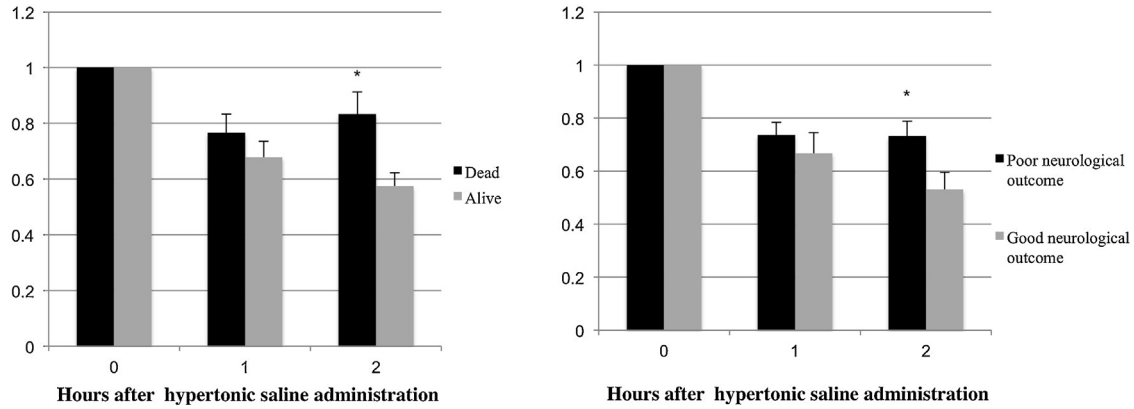

Fig. 2. Relative value of intracranial pressure after administration of first dose of hypertonic saline for intracranial hypertension. Bars show standard error of the mean. *$p < 0.05$ between groups.

Table 4
Effect of the first dose of hypertonic saline on physiologic variables by neurological outcome.

Parameter	Good neurological outcome				Poor neurological outcome			
	1 h before	At administration	1 h after	2 h after	1 h before	At administration	1 h after	2 h after
ICP	20.3	21.7	13.6*	10.8*	18.8	21.6	15.6*	15.4**
MAP	84.0	85.4	84.6	79.9	87.1	87.4	85.1	83.7
CPP	65.6	66.2	68.2	69.7	66.9	64.9	68.3	70.5

* $p < 0.05$ when compared to value at time of HTS administration.
** $p < 0.05$ when compared to 'good neurological outcome' group at same time point.

responsiveness to treatment with HTS is associated with outcome. For the purposes of this study, we chose to focus on only the first dose of HTS given for ICP > 19 as this offered the earliest information on patient responsiveness.

The mortality rate in this study is higher than usually reported at our own centre or nationally; this may be due to the inclusion of only patients receiving HTS, excluding less severely injured patients who were well-controlled with only sedation and analgesia. While in-hospital mortality is a clearly definable and commonly used endpoint for studying severe TBI, it may not be the most important, given the potential for lifelong disability and incapacitating sequelae. Many investigators now use the GOS or GOSE to assess functional outcome; a recent review [23] identified seven studies with >300 patients between 2006 and 2011 that used one of these two scores as a primary endpoint. In our study, patients who went on to have a relatively good neurological outcome showed almost twice the ICP response by 2 h after HTS treatment than those who went on to die in-hospital or be significantly disabled by long-term sequelae.

Accurate prognostication early in the course of severe TBI has proved challenging; patient populations and injuries are heterogeneous, leading to highly variable baseline prognostic risk. Data from the large IMPACT project [24] have been used to show the univariate association of known predictors like age [25], cause of injury [26], and CT scan characteristics [27] with GOS at 6 months; multivariate analysis on the same patient group suggests the potential importance of less-studied parameters like the prothrombin time and other laboratory values [9]. Other groups have used diffusion tensor imaging [28,29] or biomarkers [30,31] to predict prognosis after TBI. In a recent review, Mercier and colleagues found 41 clinical studies reporting on the prognostic value of S-100b alone [32]. Even if the absolute risk posed by the initial traumatic insult could be properly quantified, patient recovery is unpredictable and often complicated by other injuries or baseline medical condition. Our data suggests that further characterization of patient response to early treatment also may be a valuable marker for the hidden state of the injured brain. As physiologic parameters like ICP and CPP are routinely measured in patients with severe TBI, patient response may be a valuable tool for real-time prognosis and clinical judgement.

Limitations

Given the retrospective nature of this study, we were unable to discern cause-and-effect. We are only reporting an association between treatment response and eventual outcome. Not all patients had isolated TBI, potentially complicating both the reason for ICH (patient discomfort, additional manipulation due to other injuries) and response to treatment. Additionally, our sample size was relatively small, lacking power to examine treatment response among survivors alone. While hourly (or every 15 min) ICP measurements are often the best data available, they certainly do not paint a comprehensive picture of the clinical situation.

Conclusions

Patient response to treatment with the first dose of HTS for ICH is correlated with mortality and long-term neurological outcome. By 2 h after treatment, patients who went on to die or have severe long-term neurological deficits showed a rebound in ICP, while patients who fared relatively well showed sustained ICP control. We suggest that patient response to treatment is a valuable marker for injury severity, with potential utility in prognostication after TBI. Early failure to obtain a sustainable response to hyperosmolar therapy may warrant greater treatment intensity or therapy escalation.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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References

[1] Ghajar J. Traumatic brain injury. Lancet 2000;356(September (9233)):923–9.
[2] Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002–2006. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
[3] Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil 2006;21(November–December (6)):544–8.
[4] Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care, AANS/CNS, Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma 2007;24(Suppl. 1):S7–13.
[5] Härtl R, Ghajar J, Hochleuthner H, Mauritz W. Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. Acta Neurochir Suppl 1997;70:126–9.
[6] Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. Crit Care Med 2000;28(September (9)):3301–13.
[7] Bhardwaj A1, Ulatowski JA. Hypertonic saline solutions in brain injury. Curr Opin Crit Care 2004;10(April (2)):126–31.
[8] Kamel H, Navi BB, Nakagawa K, Hemphill 3rd JC, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. Crit Care Med 2011;39(March (3)):554–9.
[9] Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(February (2)):329–37.
[10] Marshall LF, Marshall SB, Klauber MR, Van Berkum Clark M, Eisenberg H, Jane JA, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma 1992;9(March (Suppl. 1)): S287–92.
[11] Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15(August (8)):573–85.
[12] Kahraman S, Dutton RP, Hu P, Xiao Y, Aarabi B, Stein DM, et al. Automated measurement of "pressure times time dose" of intracranial hypertension best predicts outcome after severe traumatic brain injury. J Trauma 2010;69(July (1)):110–8.
[13] Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 1977;47(October (4)):491–502.
[14] Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991;75(October (1)):S59–66.
[15] Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. J Neurosurg 2000;92(January (1)):1–6.
[16] Carter BG, Butt W, Taylor A. ICP and CPP: excellent predictors of long term outcome in severely brain injured children. Childs Nerv Syst 2008;24(February (2)):245–51.
[17] Sorani MD, Morabito D, Rosenthal G, Giacomini KM, Manley GT. Characterizing the dose-response relationship between mannitol and intracranial pressure in traumatic brain injury patients using a high-frequency physiological data collection system. J Neurotrauma 2008;25(April (4)):291–8.
[18] Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008;36(March (3)):795–800.
[19] Eskandari R, Filtz MR, Davis GE, Hoesch RE. Effective treatment of refractory intracranial hypertension after traumatic brain injury with repeated boluses of 14.6% hypertonic saline. J Neurosurg 2013;119(August (2)):338–46.
[20] Kerwin AJ, Schinco MA, Tepas 3rd JJ, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma 2009;67(August (2)):277–82.
[21] Stein DM, Hu PF, Brenner M, Sheth KN, Liu KH, Xiong W, et al. Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome after severe traumatic brain injury. J Trauma 2011;71(August (2)):364–73. discussion 373-4.
[22] Sheth KN, Stein DM, Aarabi B, Hu P, Kufera JA, Scalea TM, et al. Intracranial pressure dose and outcome in traumatic brain injury. Neurocrit Care 2013;18(February (1)):26–32.
[23] Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. Lancet 2012;380(September (9847)):1088–98.
[24] Maas AI, Marmarou A, Murray GD, Teasdale SG, Steyerberg EW. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. J Neurotrauma 2007;24(February (2)):232–8.
[25] Mushkudiani NA, Engel DC, Steyerberg EW, Butcher I, Lu J, Marmarou A, et al. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(February (2)): 259–69.
[26] Butcher I, McHugh GS, Lu J, Steyerberg EW, Hernández AV, Mushkudiani N, et al. Prognostic value of cause of injury in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(February (2)):281–6.
[27] Maas AI, Steyerberg EW, Butcher I, Dammers R, Lu J, Marmarou A, et al. Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(February (2)):303–14.
[28] Betz J, Zhuo J, Roy A, Shanmuganathan K, Gullapalli RP. Prognostic value of diffusion tensor imaging parameters in severe traumatic brain injury. J Neurotrauma 2012;29(May (7)):1292–305.
[29] Shah S, Yallampalli R, Merkley TL, McCauley SR, Bigler ED, Macleod M, et al. Diffusion tensor imaging and volumetric analysis of the ventral striatum in adults with traumatic brain injury. Brain Inj 2012;26(3):201–10.
[30] Böhmer AE, Oses JP, Schmidt AP, Perón CS, Krebs CL, Oppitz PP, et al. Neuron-specific enolase, S100B, and glial fibrillary acidic protein levels as outcome predictors in patients with severe traumatic brain injury. Neurosurgery 2011;68(June (6)):1624–30. discussion 1630-1.
[31] Czeiter E, Mondello S, Kovacs N, Sandor J, Gabrielli A, Schmid K, et al. Brain injury biomarkers may improve the predictive power of the IMPACT outcome calculator. J Neurotrauma 2012;29(June (9)):1770–8.
[32] Mercier E, Boutin A, Lauzier F, Fergusson DA, Simard JF, Zarychanski R, et al. Predictive value of S-100β protein for prognosis in patients with moderate and severe traumatic brain injury: systematic review and meta-analysis. BMJ 2013;346(April):f1757. http://dx.doi.org/10.1136/bmj.f1757.

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