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Pharmacologic Treatment Reduces Pressure Times Time Dose and Relative Duration of Intracranial Hypertension

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Abstract

Introduction: Past work has shown the importance of the "pressure times time dose" (PTD) of intracranial hypertension (intracranial pressure [ICP] > 19 mm Hg) in predicting outcome after severe traumatic brain injury. We used automated data collection to measure the effect of common medications on the duration and dose of intracranial hypertension. **Methods:** Patients >17 years old, admitted and requiring ICP monitoring between 2008 and 2010 at a single, large urban tertiary care facility, were retrospectively enrolled. Timing and dose of ICP-directed therapy were recorded from paper and electronic medical records. The ICP data were collected automatically at 6-second intervals and averaged over 5 minutes. The percentage of time of intracranial hypertension (PTI) and PTD (mm Hg h) were calculated. **Results:** A total of 98 patients with 664 treatment instances were identified. Baseline PTD ranged from 27 (before administration of propofol and fentanyl) to 150 mm Hg h (before mannitol). A "small" dose of hypertonic saline (HTS; $\leq$250 mL 3%) reduced PTD by 38% in the first hour and 37% in the second hour and reduced the time with ICP >19 by 38% and 39% after 1 and 2 hours, respectively. A "large" dose of HTS reduced PTD by 40% in the first hour and 63% in the second (PTI reduction of 36% and 50%, respectively). An increased dose of propofol or fentanyl infusion failed to decrease PTD but reduced PTI between 14% (propofol alone) and 30% (combined increase in propofol and fentanyl, after 2 hours). Barbiturates failed to decrease PTD but decreased PTI by 30% up to 2 hours after administration. All reductions reported are significantly changed from baseline, $P < .05$. **Conclusion:** Baseline PTD values before drug administration reflects varied patient criticality, with much higher values seen before the use of mannitol or barbiturates. Treatment with HTS reduced PTD and PTI burden significantly more than escalation of sedation or pain management, and this effect remained significant at 2 hours after administration.

Keywords

intracranial pressure, traumatic brain injury, hypertonic saline, hyperosmolar therapy

Introduction

As the availability and sophistication of care for patients with severe traumatic brain injury (TBI) have evolved, outcomes have improved and mortality has decreased.[1] Treatment in many trauma centers is now algorithmic and focuses on the prevention and treatment of the secondary insults to brain tissue that result from ischemia, inflammation, mass lesions, and/or edema. Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) can be continuously monitored, with treatment directed at maintenance of certain crucial parameters.

Many different sedatives, analgesics, and neuromuscular blocking agents are used to prevent and treat ICP elevations. Hyperosmolar agents like hypertonic saline (HTS) and mannitol are common first-line treatments for intracranial hypertension. Although there is some literature regarding sedatives, analgesia, and outcomes following TBI, there is a paucity of evidence to guide treatment on the scale of minutes to hours.

Although many sedative and analgesic agents have been studied for efficacy and effect on outcome after TBI, there is little evidence of the very short-term effects that are actually observed at the bedside and used to guide management.

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Continuous computerized monitoring and vital signs recording offer a wealth of information about the minute-to-minute physiologic status of patients with severe TBI. In previous work, we have shown the calculation of the pressure times time dose (PTD) of intracranial hypertension (ICH) from continuous, automated data to be superior to manually recorded data in prediction of eventual functional neurological outcome.[2]

We explored our extensive database of high-frequency automated vital signs data recordings to examine ICP changes before and after treatment with the pharmacologic interventions for ICH used most commonly in the neurotrauma critical care protocol at a high-volume urban trauma center. In this study, we aimed to explore whether the use of automated vital sign data can be used to look precisely at the effects of commonly used interventions for ICH.

Methods

Patients

Our institutional review board approved this retrospective data review. Study patients included all adults (>17 years old) admitted to the R Adams Cowley Shock Trauma Center Neurotrauma Critical Care Unit (NTU) January 1, 2008, through December 31, 2010, with severe TBI who required invasive ICP monitoring and on whom sufficiently complete data were available for analysis. Severe TBI was defined as postresuscitation Glasgow Coma Scale (GCS) <9 with TBI confirmed by computed tomography (CT). The automated vital signs data had already been stored and processed for this patient cohort. All drug treatment and nursing chart data were collected for this study.

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[3] according to the presence of basal cistern compression, midline shift >5 mm, and lesions >25 cm^3.

All drug treatments for increased ICP that could be identified were recorded from paper and electronic charts. These included hyperosmolar therapy, analgesia, and sedation. Analgesia was overwhelmingly provided in this patient population with a continuous infusion of fentanyl with doses between 25 and 550 μg/h. Sedation agents included propofol, lorazepam, midazolam, and dexmedetomidine. The vast majority of patients received propofol in doses of 20 to 100 μg/kg/min for sedation. Escalation above 75 μg/kg/min requires physician consent and was done for short periods only. ''Dose escalations'' represent nursing assessment that increased sedation due to agitation or increased ICP is necessary after other interventions have been attempted. These exclude temporary titrations due to registered nurse care, repositioning, and so on. These are performed according to an internal algorithm. Other agents, when used, were almost exclusively introduced after prolonged sedation with propofol. Fentanyl was given over a wide range of doses from 5 to 500 μg/h. We chose to focus on fentanyl and propofol as the use of other agents was relatively infrequent in this population.

All instances of treatment with HTS given as a bolus, mannitol, a discrete dose of a barbiturate, or an increased dose of continuously administered propofol (for sedation) or fentanyl (for analgesia) were recorded from paper and electronic records. To account for varying doses in HTS, the volume and concentration were multiplied, and doses were defined as ''small'' (≤750 or the equivalent of 250 mL 3% NaCl solution) or ''large'' (> 750 or more than 250 mL 3% NaCl solution or >100 mL of 7.5% NaCl). All but 1 dose of mannitol were 25 g; the 1 remaining dose was 50 mg. Barbiturates included were thiopental (125, 150, or 250 mg), methohexital (50, 70, 75, and 90 mg), and pentobarbital (50 and 100 mg). Treatments were correlated with recorded vital signs and included for analysis when the 5-minute mean ICP value was >20 mm Hg or nursing records indicated ICP > 20 mm Hg. This was done to exclude treatments given for reasons other than ICH.

Continuous, automated real-time vital signs data were captured through a vital sign data recorder (VSDR) from bedside monitors (GE-Marquette-Solar-7000/8000; GE Medical Systems Information Technologies, Milwaukee, Wisconsin) as previously described.[2] In short, the VSDR captures data (mean arterial pressure, ICP, CPP, heart rate, etc) every 6 seconds. Data are then transferred via a secure server and processed; 5-minute means are calculated. Artifacts are filtered by removing outliers, defined as ICP < 0 mm Hg, ICP > 100 mm Hg, CPP < 0 mm Hg, and CPP > 250 mm Hg.

The PTD values of continuous automated ICP recordings were calculated by defining PTD as the area under the curve when ICP exceeded 20 or 30 mm Hg, as illustrated in Figure 1. As seen in Figure 1, some treatment administrations were recorded at the minute of administration if the electronic medical record agreed with nursing records, while others were localized to the nearest half hour based on bedside records of administration. The percentage of time with ICP >20 or >30 mm Hg was calculated per hour using automated data.

Management Protocol

Patients with severe TBI admitted to the R Adams Cowley Shock Trauma Center are admitted to a dedicated NTU and managed according to a standardized tiered protocol in accordance with the Brain Trauma Foundation Guidelines.[4] Treatment targets the maintenance of ICP < 20 mm Hg and CPP > 60 mm Hg, as described in brief in Table 1. All patients included in the study had placement of a clinically indicated intraparenchymal monitor (Camino; Integra NeuroSciences, Plainsboro, New Jersey) or intraventricular catheter (Codman; Raynham, Massachusetts).

Statistical Analysis

Statistical analyses were performed in Excel (Microsoft; Redmond, Washington), SAS (Cary, North Carolina), and Matlab

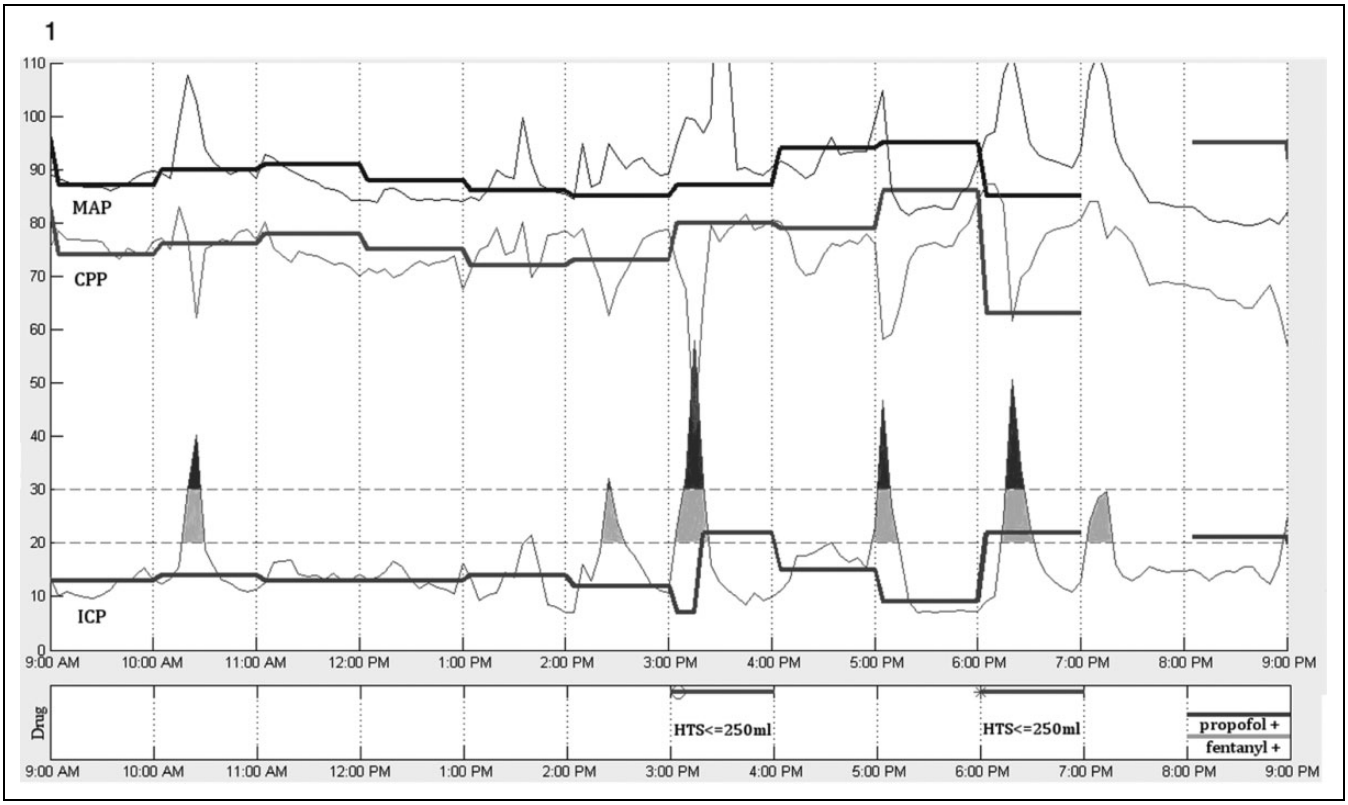

Figure 1. The bottom portion of the graph shows ICP as measured continuously (thin line) or by handwritten values in the paper chart (thick line, included for purposes of illustration only). The total "dose" of ICP >30 mm Hg is the area shaded in black, while the dose of ICP >20 mm Hg is the cumulative total area of areas shaded gray and black in mm Hg hour. MAP and cerebral perfusion pressure (CPP) are similarly shown at the top of the graph as labeled. Again, values as recorded from the nursing chart are included to illustrate the added accuracy gained when automated vital signs data are used. ICP indicates intracranial pressure; MAP, mean arterial pressure.

Table 1. Management of Patients With Severe Traumatic Brain Injury.

Initial interventions: all patients with severe TBI
Ventilate to maintain $Paco_2$ at 35-38 mm Hg
Provide supplemental O_2 to keep Pao_2 > 70 mm Hg or Spo_2 > 94%
Maintain normothermia
Optimize CPP and minimize ICP with head of bed elevation
Reduce noxious stimuli
Sedation
First tier therapies: ICP > 20 mm Hg
Increase sedation
External ventricular drainage
Hypertonic saline (3% or 7.5%); consider initial bolus of 250 mL 3% HTS
Maintain serum Osm 310-330 mOsm/L
Maintain serum sodium 150-158
Short-term hyperventilation to $Paco_2$ of 30-35 mm Hg
Second tier therapies: refractory intracranial hypertension
Decompressive craniectomy
High-dose infusion barbiturate therapy
Short-term hyperventilation to $Paco_2$ of <30 mm Hg
Measure intraabdominal pressure; consider decompressive laparotomy
Place patient in standing position

Abbreviations: CPP, cerebral perfusion pressure; HTS, hypertonic saline; ICP, intracranial pressure.

Student R2012, v8.0 (Natick, Massachusetts). Demographic data were summarized as percentages or means with standard deviation and medians with interquartile range. Student *t* test was used to compare means of ICP changes after treatment. Because multiple treatment instances were available for many patients, a linear mixed model approach was applied using the SAS procedure PROC MIXED, taking into account patient response to repeating treatment (a repeated analysis of variance). The results of P value <.05 were considered statistically significant.

Results

Continuous vital signs data were available on 98 patients who met all other inclusion criteria. Patient and injury characteristics can be seen in Table 2. In short, patients were primarily male (80.6%) and average age 39.2 $\pm$ 17.8, with a median postresuscitation GCS score of 6. Craniotomy for hemorrhage evacuation or a craniectomy for treatment of cerebral edema was required on 35 (35.7%) patients. Overall in-hospital mortality was 19.4%.

In total, 890 treatments were administered for ICP >20 mm Hg for at least 5 minutes. Discrete doses included 158 "small"

Table 2. Patient and Injury Characteristics.

	n = 98
Age, mean ± SD, y	39.2 ± 17.8
Males, n (%)	79 (80.6)
GCS, postresuscitation, median (IQR)	6 (6-7)
Marshall CT score, median (IQR)	2 (2-3)
Blunt injury, n (%)	90 (91.8)
ISS, median (IQR)	27 (24-36)
Polytrauma, n (%)[a]	42 (42.9)
Mortality, %	19.4
LOS, median (IQR), days	13.6 (10.2-19)
ICULOS, median (IQR), days	11.6 (7.8-16.4)
Craniotomy/craniectomy, n (%)	35 (35.7)

Abbreviations: GCS, Glasgow Coma Scale; CT, computed tomography; ISS, injury severity score; LOS, length of stay; ICU, intensive care unit; SD, standard deviation; IQR, interquartile range.
[a]Defined as nonhead ISS > 15.

and 71 "large" doses of HTS, respectively. In all, 66% of the doses classified as small were 250 mL of 3% HTS, while 89% of the large were given as 500 mL 3% HTS. Seven doses of mannitol were administered. Dose escalations were recorded 325 times for propofol, 216 times for fentanyl, and 89 times for propofol and fentanyl together. There were also 23 administrations of a discrete dose of a barbiturate.

Figure 2 shows the PTD of ICP >20 mm Hg (PTD_{20}) in the hours before, during, and after treatment administration. Values from 1 to 4 hours after administration reflect a statistical mixed model to account for the effect of multiple sampling in some patients. The PTD_{20} values in the hour of treatment administration with both dose sizes of HTS, propofol, fentanyl, and propofol + fentanyl were statistically the same, while these values in the hour of administration of mannitol or barbiturates were approximately 5 and 2.5 times higher, respectively. A small dose of HTS reduced PTD_{20} by 34.0% in the first hour, but by the second hour PTD_{20} was not different from baseline. A large dose of HTS reduced PTD by 56.3%, 78.6%, and 41.4% after 1, 2, and 3 hours, respectively. Pressure times time dose did not change significantly after administration of propofol, fentanyl, or a combination of the 2. No significant change was seen in PTD_{20} after administration of a dose of barbiturates.

The percentage of time per hour with ICP > 20 mm Hg (PTI_{20}) before and after treatment can be seen in Figure 3. In the hour of treatment, patients spent an average of 33.6% (before fentanyl) to 78.0% (before mannitol) of the hour with ICP >20 mm Hg, per continuous ICP monitoring. Baseline PTI_{20} was statistically comparable before administration of HTS, propofol, fentanyl, or propofol and fentanyl, while patients receiving barbiturates or mannitol showed significantly higher values. The PTI_{20} was 36.5% lower 1 hour after a small dose of HTS and remained 30.8% lower than baseline at 2 hours. The PTI_{20} decreased by 36.8% and 83.0% 1 or 2 hours after administration of a large dose of HTS, respectively. The PTI_{20} remained significantly depressed for 4 hours after administration of either dose of HTS. As seen in the figure, PTI showed modest but significant reductions after treatment with propofol or fentanyl. There were no significant changes in ICP or CPP after treatment with mannitol or a barbiturate.

Conclusion

Treatment for severe TBI is algorithmic and aims for the maintenance of measureable parameters within ranges assumed to be beneficial to most patients. With few well-designed and controlled prospective trials of treatment for severe TBI on record or even now ethically possible, clinical decisions are aided by best-practice guidelines and expert consensus.

The availability of continuous vital signs data allows for a detailed and more accurate assessment of ICP. The concept of "PTD" of ICP has been explored previously by our group. Kahraman et al found a lack of agreement between PTD measured automatically and calculated from nursing records; they also found automated measurement of PTD to have higher predictive power for eventual clinical outcome than manually recorded measurements, suggesting that automated recording is capturing features of patient clinical course that are lost with less granular information.[2] Sheth et al also found increased PTD to correlate with mortality and poor functional outcome.[5] Most studies measuring treatment effect in ICH measure the absolute change in ICP in a certain time interval after treatment. The ability to calculate the dose of ICP >20 mm Hg or the percentage of time with ICH allows us to better characterize the ability of medication to reduce exposure to potentially harmful values of ICP.

We chose to look for treatment effect with the drugs most commonly used for ICP control in our clinical practice; however, this is complicated by the different methods of administration and dosing. Propofol and fentanyl are administered as continuous infusions, and so we chose to look at dose escalations, as each represented a clinical decision to escalate care following a sedation algorithm. The HTS, mannitol, and barbiturates were included only when administered as bolus doses as this reflects our clinical practice.

Although other sedative agents are used in our NTU, propofol is by far most commonly used for maintenance sedation. Propofol is a phenol derivative with a quick onset of action and rapid plasma clearance, allowing for precise dose control and relatively rapid return to baseline for neurological evaluations. Although sedation is necessary for ICP control in ventilated patients with TBI, there is some evidence that propofol itself plays a role in at least short-term[6] neuroprotection against cerebral ischemia[7,8] and edema.[9,10]

Several trials have compared the relative efficacy of propofol with other sedatives, including morphine[11] and midazolam,[12] with outcomes including therapeutic intensity, daily ICP, and plasma concentration of markers of inflammation. However, short-term ICP changes after propofol administration have not been systematically studied. In our study, an increased dose of propofol led to a modest (but statistically insignificant) change in PTD_{20}, with a concomitant significant sustained decrease in PTI_{20} of 17.6% and 15.0% after 1 or 2 hours.

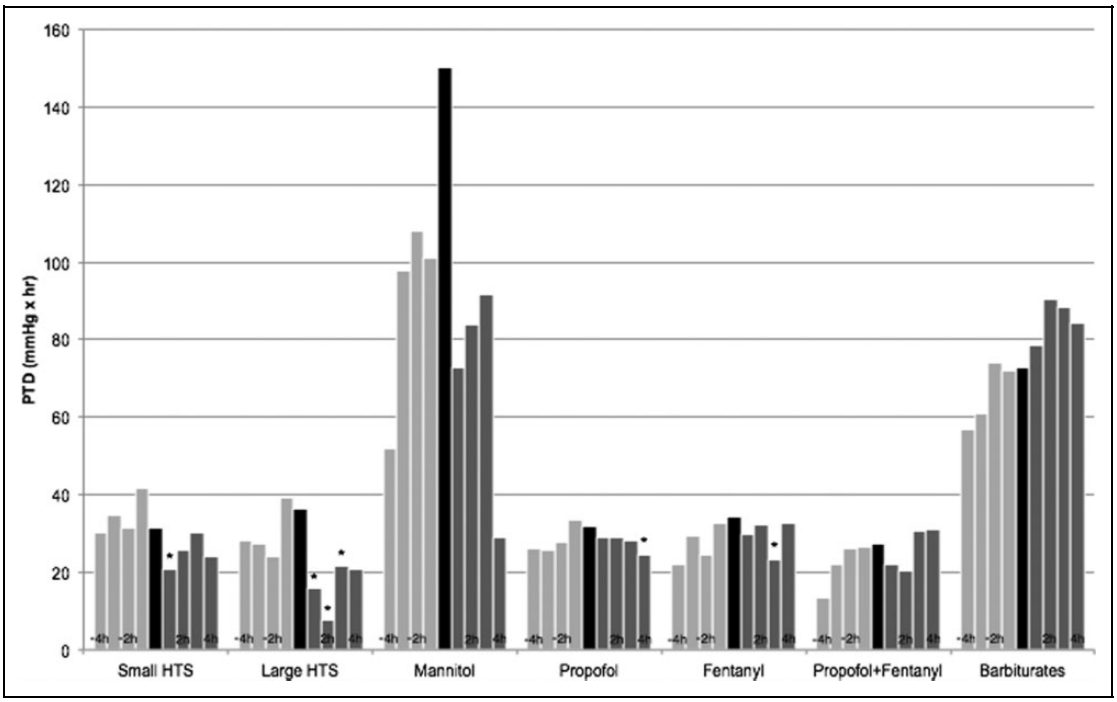

Figure 2. "Pressure times time" dose of intracranial pressure (ICP) >20 mm Hg before and after treatment. *P* < .05 when compared to baseline (middle bar).

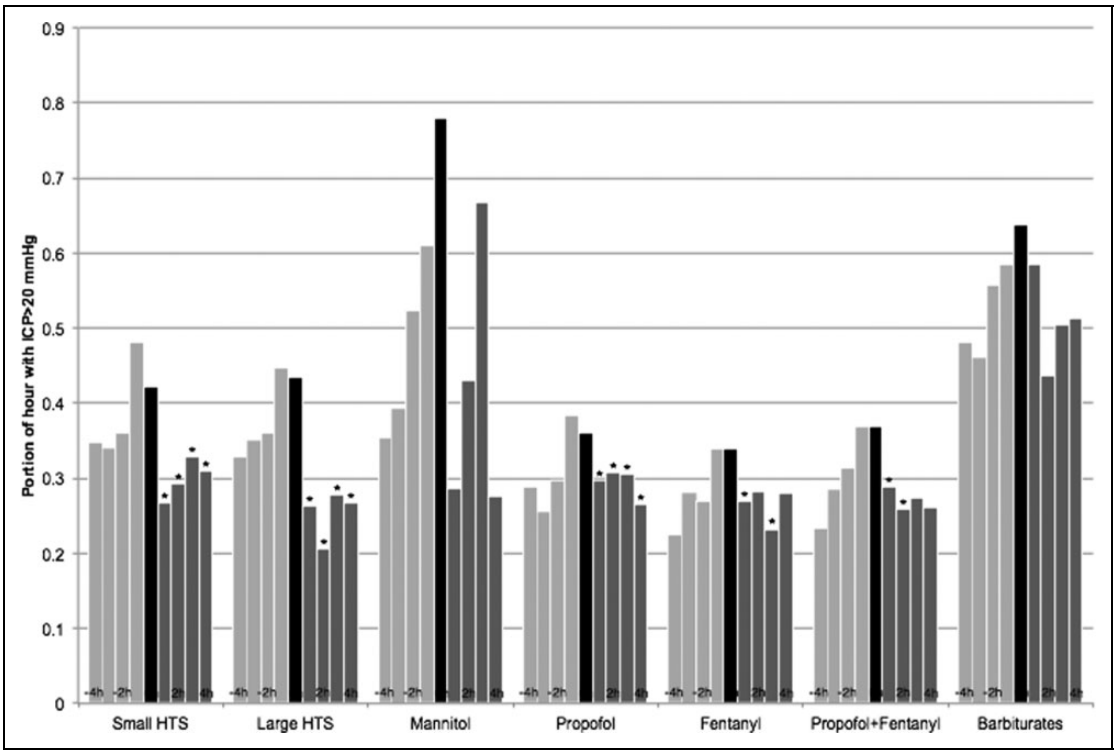

Figure 3. Portion of time with intracranial pressure (ICP) > 20 mm Hg per hour before and after treatment. **P* < .05 when compared to baseline (middle bar).

The effects of fentanyl and other opioids on ICP and CPP are as yet unresolved. A recent review[13] identified 5 randomized control trials[14-18] that examined the effect of a bolus or brief infusion of opioids on ICP and CPP. Of the 5, 3 found that ICP increased and CPP decreased after opioid administration.[15,17,18] Lauer et al[16] found no effect on either ICP or CPP,

while White et al[14] found that fentanyl blunted but did not prevent the ICP increase accompanying endotracheal tube suctioning. A more recent study administered ascending doses of remifentanil before endotracheal tube suctioning; as dosing increased, more patients required vasopressor support to maintain adequate CPP. The ICP increases were also seen after suctioning, consistent with autoregulation secondary to hypotension induced by the study drug.[19]

Our data showed no statistically significant change in PTD_{20} within 2 hours after increasing the dose of fentanyl. However, PTI_{20} did change significantly, with 20% less time spent with ICP >20 mm Hg in the first hour after administration. These results from continuously monitored data suggest that the administration of fentanyl may indeed either (subtly) lower ICP directly or blunt patient ICP response to ongoing factors like pain, stressors, or clinical interventions that would have caused spikes of ICP. A prospective study utilizing continuous vital signs recording could be of great benefit in the future in clarifying what appears to be this relatively modest effect of fentanyl on ICP.

Hyperosmolar agents have long been recognized for the treatment of cerebral edema, with HTS gaining popularity in recent decades.[20-23] In this set of 98 patients, we saw 229 instances of treatment with HTS when ICP >20 mm Hg, and only 7 doses of mannitol under the same conditions—a ratio that speaks to clinical practice and judgment at our institution. While mannitol is used in acute resuscitation (not captured in these data), it was used exceedingly rarely in patients with severe TBI once admitted to the NTU. The average baseline dose of ICP >20 mm Hg is also ~5 times higher in patients receiving mannitol versus those receiving HTS, suggesting a much more dire clinical picture. With this in mind, mannitol reduced ICP dose >20 mm Hg by ~50% in the first hour after administration (not statistically significant), after which the ICP dose-trended back up.

Hypertonic saline significantly reduced both ICP dose and percentage of time with ICP >20 mm Hg for up to 4 hours after administration. Hypertonic saline doses were stratified according to size, with the usual initial dose of 250 mL 3% NaCl solution considered "small" and amounts greater than this considered "large." Intracranial pressure decrease was both more pronounced and lasted longer after a "large" dose of HTS (with a significant difference in PTD20 for 3 hours after administration), when compared with the "small" dose. At 2 hours after HTS administration, the relative decrease in PTD20 was approximately 4 times larger after a larger dose of HTS.

This study has a number of limitations imposed chiefly by the constraints of being a retrospective data review from a single center, albeit a large one. In this patient population, some drugs were much more or less prevalent; notably, mannitol was used only 7 times when ICP > 20 mm Hg for at least 5 minutes. Unfortunately these baseline differences make it impossible to compare the efficacy of the hyperosmolar agents utilized in this population. Since we are unable to validate justification for medication choices throughout treatment, we measured ICP changes after 2 conditions were met: ICP > 20 mm Hg for at least 5 continuous minutes and a treatment commonly used to control ICP was given. This method may be incorrectly correlating a treatment instance and a clinically unnoticed period of ICH. As in any retrospective drug study, we also acknowledge that there are likely time differences between the reality of drug administration in a busy clinical environment and the recorded event. Although previous studies have not agreed on the effect of fentanyl and propofol specifically in the control of ICP, this study does suggest that both are capable of controlling ICP. However, this study is not meant to guide treatment choice, as the results are not generalizable and are limited by study design. Rather we hope to show that treatment effect can be calculated with more nuanced indices of ICP (PTD and PTI) and suggest that these results could be translated into real-time clinical assessments.

Continuous monitoring of vital signs and physiologic parameters has advanced the capabilities of critical care. However, the ability to quantify patient response to treatment—in real time—would provide an invaluable objective measure for physicians. Just as monitors in some centers are able to give visual clues about current physiologic status, we propose that an index of treatment responsiveness could prove similarly useful. The ability to monitor treatment response in real time could inform pharmacologic choice and timing—imagine if a physician could look at objective data for which patients are most responsive to disparate medical therapies. Using new techniques like the calculation of PTD and PTI could help with the characterization of ICP changes during and after treatment that would be integral to this endeavor. The PTD and PTI represent a more nuanced view of ICH than can be expressed by a single displayed ICP value—these reflect the calculations that a clinician does inherently when looking at a time-trended variable. In this study, we have used novel methods to examine the characteristics of short-term ICP changes associated with administration of some of the most commonly used medications for the sequelae of severe TBI.

Authors' Note

The views expressed in this article are those of the authors and do not necessarily represent the official position or policy of the Air Force, the Department of Defense, or the US Government.

Declaration of Conflicting Interests

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