Intracranial pressure response after pharmacologic treatment of intracranial hypertension

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BACKGROUND

Severe traumatic brain injury (TBI) is the leading cause of death after injury, despite advances in treatment and monitoring. (1) Physiologic vital signs, including intracranial pressure (ICP) and cerebral perfusion pressure (CPP), are monitored continuously in the critical care setting. Automated, high-frequency monitoring systems are capable of capturing and recording massive amounts of this valuable physiologic data. However, vital information is typically still collected manually at pre-determined intervals that may not reflect a rapidly changing clinical situation.

Treatment of patients with severe TBI aims to prevent or mitigate secondary injury consisting of cerebral edema, inflammation, and ischemia. Treatment administrations represent periods of particular clinical interest when documentation is integral to effective evaluation. In most centers treatment for intracranial hypertension is tiered, with "first tier" interventions (hyperosmolar therapy, increased sedation, external ventricular drainage, short-term hyperventilation) and more aggressive "second tier" interventions (hyperventilation to a $PaCO_2$ of less than 30 mmHg, high-dose barbiturates, surgical decompression). (2) Clinical practices to achieve these goals vary between centers and there is little data on the short-term effects of commonly used pharmacologic agents.

Hyperosmolar therapy with mannitol (3, 4, 5, 6) or hypertonic saline (HTS) (7, 8, 9, 10, 11) is well-recognized to aid in ICP control. While some studies show similar effects of equimolar doses of mannitol and HTS on ICP control (12, 13) others suggest that HTS offers

potential superiority (9, 14, 15, 16). In our practice these agents are commonly administered as boluses, with HTS less commonly administered as a continuous infusion.

A variety of sedatives and analgesics are employed to ameliorate pain and agitation in patients with severe TBI. The Brain Trauma Foundation found only one study fulfilling inclusion criteria for their management guidelines, performed by Kelly et al. (17) This study compares endpoints (mortality, Glasgow Outcome Scale) after the use of propofol or morphine sulfate, but also measures clinical endpoints; the study found ICP to be lower by day 3 in the propofol group. There have been no systematic studies of the short-term effects of propofol on ICP, although it is commonly utilized clinically to aid in ICP control. Similarly, the few existing randomized trials that examine the effects of opioids on ICP or CPP are conflicting and at best suggest minor improvements in ICP control (18, 19, 20, 21, 22).

We hypothesized that the short-term effects of pharmacologic interventions for increased ICP could be measured with continuous, automated vital signs data and that this is a more accurate representation of the clinical picture than manually recorded measurements.

METHODS

Patients

Study subjects were admitted to the R Adams Cowley Shock Trauma Center, a high volume academic urban trauma center, between 2008 and 2010. The Institutional Review Board

(IRB) approved the collection of retrospective data on patients older than 17 years of age admitted to the Neurotrauma Critical Care Unit (NTCC) with severe TBI who required invasive ICP monitoring. Severe TBI was defined as post-resuscitation Glasgow Coma Scale (GCS) <9 with TBI confirmed by computed tomography (CT).

Management Protocol

Patients with severe TBI admitted to the R Adams Cowley Shock Trauma Center are admitted to a dedicated NTCC and managed according to a standardized tiered protocol in accordance with the Brain Trauma Foundation Guidelines. (23) Treatment targets the maintenance of ICP < 20 mmHg and CPP > 60 mm Hg, as described previously and shown in Table 1. (24) All patients included in the study had placement of a clinically indicated intraparenchymal monitor (Camino®; Integra NeuroSciences) or intraventricular catheter (IVC; Codman; Raynham, MA).

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 according to the presence of basal cistern compression, midline shift >5mm, and lesions >25 cm3 (25) by a blinded reviewer. Outcomes measured included in-hospital mortality, overall length of stay, and length of stay in the intensive care unit.

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 25-550 mcg/hr. Sedation agents included propofol, lorazepam, midazolam, and dexmedetomidine. The vast majority of patients received propofol in doses of 20-100 mcg/kg/min for sedation. Other agents, when used, were almost exclusively introduced after prolonged sedation with propofol. 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 hypertonic saline (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 one dose of mannitol were 25 g; the one remaining dose was 50 mg. Barbiturates included were thiopental (125 mg, 150 mg, or 250 mg), methohexital (50 mg, 70 mg, 75 mg, 90 mg), and pentobarbital (50 mg, 100 mg). Treatments were correlated with recorded vital signs and included for analysis when the 5-minute mean ICP value was >20 mmHg or nursing records indicated ICP>20 mmHg. This was done to exclude treatments given for reasons other than ICH.

Continuous, automated real-time vital sign data were captured through a vital sign data recorder (VSDR) from bedside monitors (GE-Marquette-Solar-7000/8000) as previously described. (24) In short, the VSDR captures data (systolic and diastolic blood pressure, intracranial pressure, cerebral perfusion pressure, heart rate, etc.) every 6 seconds. Data are then transferred via a secure server and processed; five minute means are calculated. Artifacts are filtered by removing outliers, defined as ICP<0 mmHg, ICP>100 mmHg, CPP<0 mmHg, and CPP>250 mmHg. Vital signs were also transcribed from paper charts; ICP, CPP, and mean arterial pressure (MAP) are noted each hour, except for when ICP>20 mmHg, when ICP is recorded every 15 minutes per protocol. Nursing staff see real-time, continuous data on the clinical monitors at the bedside.

Statistical Analysis

Statistical analyses were performed in Excel (Microsoft; Redmond, WA), SAS (Cary, NC) and Matlab Student R2012, v8.0 (Natick, MA). Demographic data were summarized as percentages or means with standard deviation and medians with interquartile range. The Student's t test was used to compare mean ICP values. A statistical mixed model was applied ICP values after treatment administration to account for multiple sampling. Probability values for results being due to chance (p) of <0.05 were considered statistically significant.

RESULTS

117 patients met inclusion criteria. Patient and injury characteristics can be seen in Table 2. Briefly, patients were primarily male (79.4%), average age 40.0 ± 17.7 with a median post-

resuscitation GCS score of 6. The most common mechanism of injury was motor vehicle or motorcycle crash, affecting 51 patients (44% of the sample), followed by 32 patients suffering a fall. Overall in-hospital mortality was 18.8%.

450 treatments were administered in this patient population when the nursing record indicates ICP>20 mmHg, as detailed in Table 2. 968 treatments were administered during an hour in which automated, continuous data registered at least 5 consecutive minutes of ICP>20 mmHg. To ascertain whether comparisons could be made between these sets of treatments administrations, 386 instances of treatment were identified when both the manual record indicated ICP>20 mmHg and the automated data included ICP>20 mmHg for at least 5 minutes. ICP changes as calculated from manual or continuous data were compared within this matched set. Figure 1 shows a representative 12-hour period of ICP monitoring in one patient. Manually recorded and automated ICP are shown in thick and thin lines, respectively. Manual recordings are made every 15 minutes when ICP>20 mmHg. A dose of HTS is indicated in the bottom bar by a circle (beginning of transfusion) and line (duration).

Table 3 shows the mean ICP in the hour before treatment with each of the analyzed interventions. Mean ICP before HTS, an increase in dose of propofol, fentanyl, or a combination of increase in dose of both propofol and fentanyl ranged from 18.51-19.99 mmHg according to automatic data and from 20.46-22.63 mmHg in nursing records. Mannitol and barbiturates were given after average ICP values ranging from 26.13-33.45 mmHg in the hour before treatment. Dose increases varied between 5-75 mcg/kg/min, with relative increases of 5-650%. Fentanyl dosing ranged from 25-550 mcg/hr, with dose increases of 20-300 mcg/hr (16-650% relative

increase). No correlation was seen between absolute or relative dose increase and ICP decrease after treatment.

Figure 2 shows ICP changes according to the nursing and automated records after treatment with hyperosmolar therapy. Figure 3 shows ICP changes after escalation of sedation or analgesia. All treatments resulted in significant ICP changes after one or two hours except for mannitol and barbiturate administration. Notably, there were only 8 (in automated data) or 7 (in the nursing records) instances of mannitol administration in this patient population. There was no significant change in mean ICP after mannitol administration. Barbiturates were also used relatively sparingly in this patient population, with 20 instances recorded when manual records indicate ICP>20 mmHg and 24 when continuous data shows ICP>20 mmHg for 5 minutes. No statistical difference was seen between different doses of mannitol (25 g or 50 g) or different drugs and doses of barbiturates.

ICP fell after administration of a 'small' dose of HTS by 8.83 mmHg in the first hour and 9.76 mmHg in the second according to manual data. Automated data indicated a decrease of 3.04 and 5.48 mmHg in the first and second hours, respectively. Large doses of HTS showed similar trends. Propofol escalations resulted in an ICP decrease of 7.3 mmHg (manual) or 1.58 mmHg (automated) in the first hour. Similarly, fentanyl resulted in ICP decreases of 8.22 mmHg (manual) and 3.77 mmHg (automated) in the first hour of treatment. A simultaneous increase in fentanyl and propofol resulted in a change of 7.09 mmHg (nursing) or 2.15 mmHg (automated). While ICP continued to fall in the second hour after administration of HTS, mannitol, or

barbiturates, it rose insignificantly in the same time period after administration of propofol or fentanyl.

The ICP changes shown are based on overlapping but not identical sets of treatment instances. To validate the similarity of the sets of treatment instances, a nested set analysis was performed on the set of 386 treatments that were administered when both the nursing and automated records indicate that ICP>20 mmHg. There were no significant differences in ICP changes after treatment between the full set and subset for any treatment type. ICP change after treatment with small or large doses of HTS, or elevations in propofol and fentanyl were significantly different when calculated with manual or continuous data within this matched set. There is no significant difference between manual and continuous data when looking at matched instances of barbiturate (n=15) and mannitol (n=7) administration.

DISCUSSION

The availability of high-frequency automated, continuous ICP data allows for a detailed examination of ICP changes after treatment with common pharmacologic agents used to treat patients with severe TBI. Little current data exists on the effects of these therapies on ICP, despite widespread clinical use.

While ICP is monitored continuously at the bedside, busy clinical staff are unable to observe all changes in real time. To this end, vital signs (ICP, CPP, MAP) are recorded hourly by trained nursing staff in the bedside record, with ICP recorded every 15 minutes when >20

mmHg per our institutional protocol. If an intraparenchymal monitor is present, continuous monitoring is visible at the bedside, while an IVC requires clamping before an accurate measurement can be observed. Whether this manual documentation is clinically adequate has been explored previously by several groups, including our own. An early study found the nurse "end-hour" ICP value to be a reasonable estimate for mean ICP over the past hour. (26) Venkatesh et al found a strong correlation between end-hour and 15-minute ICP values in 16 patients. (27) All measurements in this study were manually recorded, however. Zanier et al showed that while computer-generated end-hour data accurately reflects manually recorded values, ICH tended to be underestimated in patients showing ICP instability. (28) Most recently, Kahraman et al compared the area under the curve of ICP when ICP>20 mmHg between automated and manual measurements and found poor agreement and also found that the automated values were better predictive of eventual functional neurological outcome. (24) Zanier and Kahraman's studies suggest that automated monitoring captures elements of patient physiologic status that are lost in manual documentation.

In this study, we sought to answer first, what ICP changes were seen after common treatments for ICH, and second, whether these changes were accurately characterized by the ICP values in the manual record. In most centers, while continuous ICP monitoring is displayed at the bedside, it is not technologically intuitive to accurately appreciate ICP changes over larger periods of time. Treatment administration marks a discrete period of time over which ICP changes are of particular interest, as treatment of severe TBI is directed at maintenance of ICP, CPP, and other physiologic measurements within discrete parameters as outlined by evidence-

based guidelines. (23) Judgment of the relative success of an ICP-directed therapy relies, of course, on the methods used to evaluate response.

We found more than twice as many treatment administrations when correlating treatments with continuous data than with hand-written, and this proportion was markedly higher in instances of propofol escalations, which nursing staff can administer according to a sedation protocol without physician notification. The simplest explanation for this is that there are short periods of ICH that staff are reacting to without documentation - the presence of ICP-related treatment suggests that actions are being taken based on real-time clinical monitoring that does not get recorded manually.

The mean ICP before treatment is indicative of both patient status and prior treatment effectiveness. The average ICP before treatment with HTS or propofol or fentanyl dose escalations was quite similar when looking at either automated or nursing data (no statistic difference between baseline ICPs in each group). The mean ICP in the hour before these treatments were given was marginally less than 20 mmHg when calculated from continuous data, suggesting ICP fluctuations around that treatment-triggering cutoff. Mannitol and barbiturates were given when patients had significantly higher mean ICP values – reflecting a clinical decision to use these agents for more severe ICH.

Hypertonic saline administration resulted in the largest significant decrease in ICP when compared to the other treatments, and mean ICP continued to decrease in the second hour after therapy. Mannitol, used in acute resuscitation but sparingly in this patient population, resulted in

no statistically significant change in ICP – and when automated data was used for analysis, mean ICP trended higher after administration. The disparate mean baseline ICP values before administration of HTS or mannitol make it impossible to compare therapeutic effect directly.

Interestingly, ICP decreased significantly after an increased dose of continuously infused propofol or fentanyl. Propofol is widely used as a sedative agent with rapid onset and short duration of onset. Several older studies found minor ICP decreases after prolonged propofol infusion. (29, 30) In a randomized controlled trial, Kelly et al compared endpoints for patients sedated with either propofol or morphine sulfate, and found improved ICP control and lower therapeutic intensity in the propofol group. (17) The rapidly-metabolized narcotic fentanyl is also commonly deployed but with relatively unclear effects on ICP. To our knowledge this is the first report of the therapeutic effects of propofol or fentanyl using continuous, high-frequency data. Our data show that dose escalations of propofol or fentanyl result modest but significant decreases in ICP over the following two hours.

After almost all included treatments, ICP decreases measured with continuous data were about half those calculated from nursing records. However, the discrepancy between manual and continuous data was largest for the treatments administered as elevations in dose of a continuous infusion. The estimated ICP decrease after propofol, for instance, was ~4.5x larger when calculated with handwritten ICP values than when continuous automated data is used. While clinicians are necessarily acting on more evidence than the few numbers recorded by hand, this does suggest that we are overestimating the effect of these common treatments, especially over time periods longer than the minutes one could reasonably expect someone to

remain at the bedside watching a monitor. A clinician may observe an initial favorable response in ICP that is obviated by a later, unobserved rebound in ICP. Our data suggest that the current commonly used methods of measuring treatment response do not accurately reflect clinical events.

In a 2007 report from the Maryland Nursing Workforce Commission, 81% of surveyed nurses indicated that patient care documentation directly affected the amount of time spent in direct patient care. (31) Of those, 54% said they spent between a quarter and a half of their shift on documentation, and 29% reported spending more than half of their shift on documentation. Over the time period of this study, 8 pages of documentation were produced by routine nursing activities alone per day. The data in the current study suggest that manual vital signs documentation in neuro-intensive care is inferior to automated data collection for some purposes. In a setting with heavy nursing workload, documentation must be effective and efficient – and when automated monitoring is already present, more intuitive data visualization could ameliorate this redundancy.

Our group has previously made advances in the bedside display of new and intuitive measures of physiologic status in the setting of neurotrauma critical care. (32) These monitors are designed to allow clinicians to quickly assess both current status and historical trends using graphic, colored displays. Groups in cardiovascular (33, 34, 35), hematologic, (36) and emergency medicine (37) have developed "track and trigger" systems that ideally trigger medical responses to patient instability, but efforts have been hampered by concomitant increased nursing workload and calculation and trigger interpretation variability. One group reported on the

implementation of an integrated monitoring system that continuously monitors multiple parameters indicative of patient cardiorespiratory stability, and found their calculated instability index to correlate well with established instability criteria. (37) Efforts like these demonstrate the utility of integrating continuous data capture into smarter integrated systems that can tease out trends before they are clinically overt.

Due to the retrospective nature of this study, we are unable to assume intent to treat ICH, but can only look at ICP changes in patients with evidence of ICH before treatment. This is of course making assumptions about the correlation between treatment and ICH. It is entirely possible, especially with the administration of increased doses of propofol and fentanyl, which are not used solely for ICP control, that these were given for unrelated purposes. We also readily acknowledge that data recorded in the handwritten chart is not comprehensive and does not reflect clinicians' more nuanced understanding of their patients' current physiological status.

CONCLUSION

In a population of patients with severe TBI, we have shown that ICP changes after routine pharmacologic intervention can be calculated from both handwritten charts and continuous, automated data, and that the data from handwritten charts dramatically overestimates treatment effect. Of the therapies examined, administration of hypertonic saline resulted in the largest significant decrease in ICP. Improved real-time analysis of treatment effect is possible using continuous vital signs monitoring and could provide valuable and intuitive clinical information.

	n=117
Age (y), mean ± SD	40.0 ± 17.7
Males, n (%)	93 (79.4)
Mechanism of injury, n (%)	
Motor vehicle/motorcycle crash	51 (44)
Fall	32 (27)
Pedestrian struck	13 (11)
Assault	16 (14)
Other	5 (4)
Blunt injury, n (%)	103 (88.0)
GCS, post-resuscitation, median (IQR)	6 (5-7.5)
Marshall CT score, median (IQR)	2 (2-3)
ISS, median (IQR)	29 (25-38)
Polytrauma, n (%)*	46 (39.7)
In-hospital mortality, n (%)	22 (18.8)
LOS (days), median (IQR)	14.0 (10.7-18.7)
ICULOS (days), median (IQR)	11.6 (8.5-16.7)
Craniotomy/ Craniectomy, n (%)	35 (35.7)

*Defined as non-head ISS>15
GCS=Glasgow Coma Scale; CT=computed tomography; ISS=Injury Severity Score; LOS=Length of stay; ICU=Intensive Care Unit.

Table 1. Patient and injury characteristics.

Treatment	**Nursing**	**Automated**	**Both**
Small HTS	86	165	79
Large HTS	89	117	72
Mannitol	8	7	7
Propofol	139	343	115
Fentanyl	75	219	68
Propofol and fentanyl	33	93	30
Barbiturate	20	24	15

Table 2. Instances of treatment when intracranial pressure is greater than 20 mmHg, as defined by the presence of a manually recorded value >20 mmHg (nursing) or at least 5 minutes of consecutive ICP>20 mmHg recorded by the automatic vital signs data recording system (automated).

Treatment	Mean ICP (manual records), mmHg	Mean ICP (automated data), mmHg
Small HTS	20.91	19.35
Large HTS	21.50	19.99
Mannitol	26.22	33.45
Propofol	20.46	19.10
Fentanyl	21.43	18.98
Propofol and fentanyl	22.63	18.51
Barbiturate	26.14	26.61

Table 3. Mean intracranial pressure (ICP) in the hour before treatment with hypertonic saline (HTS), mannitol, barbiturates, or an increased dose of continuously infused propofol and/or fentanyl.

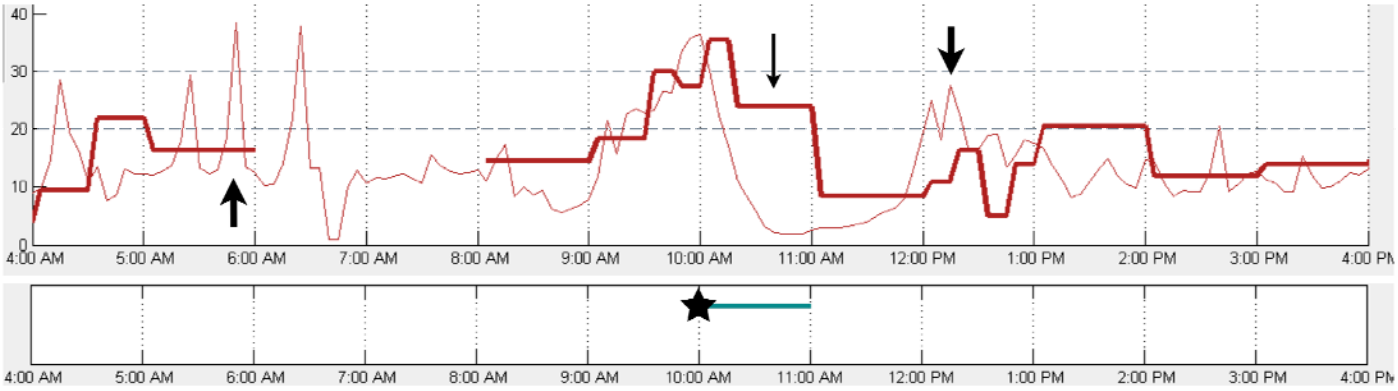

Figure 1. A visualization of manually recorded (thick line) and continuously monitored (thin line) intracranial pressure over 12 hours. ICP (mmHg) is on the vertical axis. The bottom bar shows administration of hypertonic saline at 10:00AM (star). The thin arrow indicates the time-lag of manual data. The thick arrows show periods of intracranial hypertension not captured in the manual record, that in this case likely contribute to over-estimation of treatment effect in the manual documentation.

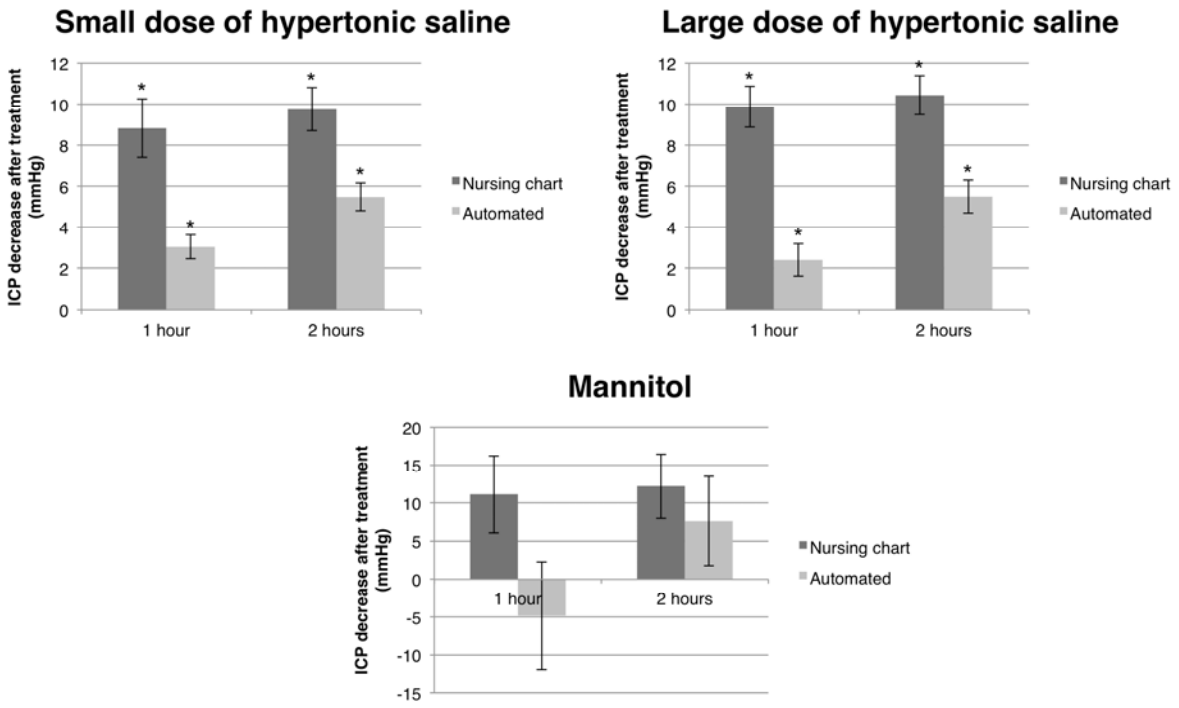

Figure 2. ICP decrease after treatment with hyperosmolar agents. HTS doses are designated as 'small' (≤ the equivalent of 250 ml 3% NaCl solution) or 'large' (>250 ml 3% NaCl solution). Bars indicate standard error.

* $p<0.05$ when compared to baseline intracranial pressure value.

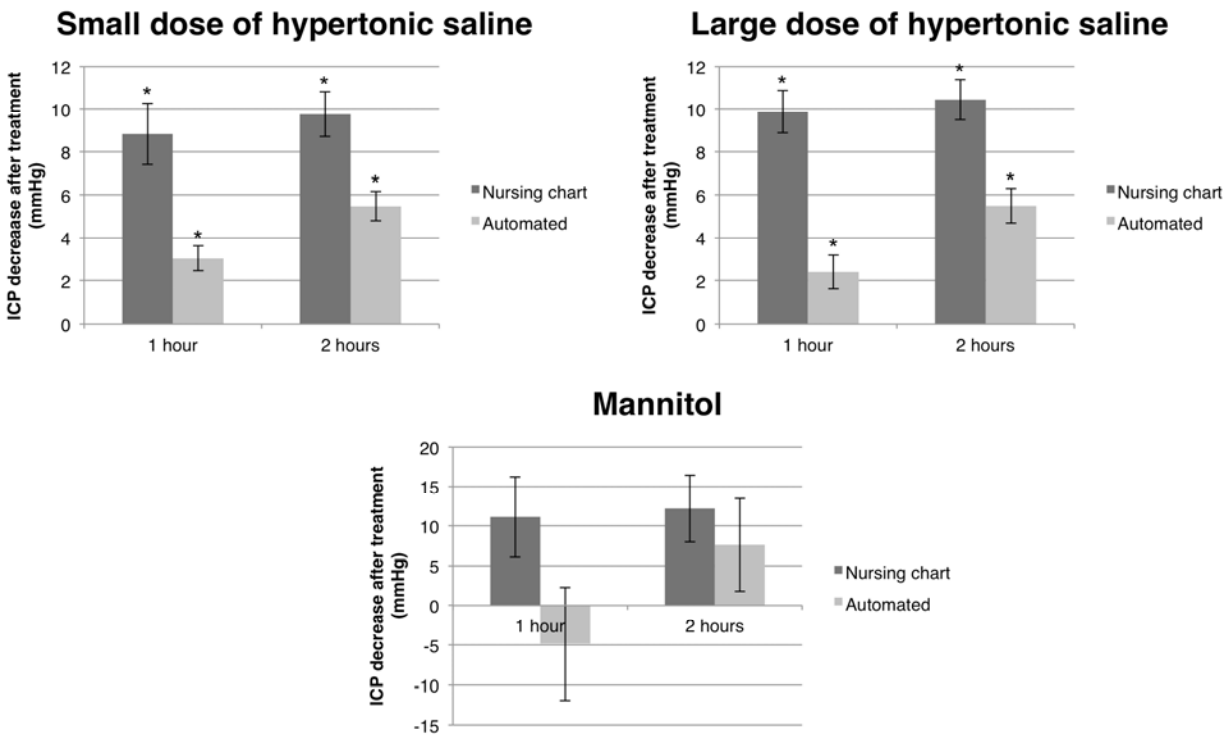

Figure 3. ICP decrease after additional treatment with sedative/analgesic agents. Barbiturates were administered as discrete doses, while propofol and fentanyl were given as dose escalations of continuous infusions. Bars indicate standard error.

* $p<0.05$ when compared to baseline intracranial pressure value.

Author contribution

Chart review, data processing, and data analysis were performed by K Colton and S Yang. PF Hu performed data filtration and analysis. HH Chen performed statistical analysis. The manuscript was written by K Colton, B Bonds, and DM Stein. DM Stein and T Scalea supervised the project and provided invaluable clinical support.

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