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Effectiveness of Pharmacological Therapies for Intracranial Hypertension in Children with Severe Traumatic Brain Injury – Results from an Automated Data Collection System Time-Synched to Drug Administration

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Abstract

Objective—To describe acute cerebral hemodynamic effects of medications commonly used to treat intracranial hypertension in children with traumatic brain injury (TBI). Currently, data supporting the efficacy of these medications are insufficient.

Design—In this prospective observational study, intracranial hypertension (intracranial pressure [ICP] ≥ 20 mm Hg for > 5 min) was treated by clinical protocol. Administration times of medications for intracranial hypertension (fentanyl, 3% sodium chloride [HTS], mannitol and pentobarbital) were prospectively recorded and synchronized with an automated database that collected ICP and cerebral perfusion pressure (CPP) every 5 seconds. ICP crises confounded by external stimulation or mechanical ventilator adjustments were excluded. Mean ICP and CPP from epochs following drug administration were compared to baseline values using Kruskal-Wallis ANOVA and Dunn's test. Frailty modeling was used to analyze the time to ICP crisis resolution. Mixed effect models compared ICP and CPP 5min after the medication vs. baseline, and rates of treatment failure.

Setting—A tertiary care children's hospital.

Patients—Children with severe TBI (Glasgow Coma Scale score ≤ 8).

Interventions—None.

Measurements and Main Results—We analyzed 196 doses of fentanyl, HTS, mannitol and pentobarbital administered to 16 children (median: 12 doses/patient). Overall, ICP significantly

decreased following fentanyl, HTS and pentobarbital. After controlling for administration of multiple medications, ICP was decreased following HTS and pentobarbital administration; CPP was decreased following fentanyl and was increased following HTS. After adjusting for significant covariates (including age, GCS score and ICP), HTS was associated with a two-fold faster resolution of intracranial hypertension than either fentanyl or pentobarbital. Fentanyl was significantly associated with the most frequent treatment failure.

Conclusions—ICP decreased after multiple drugs, but HTS may warrant consideration as the first-line drug for treating intracranial hypertension, as it was associated with the most favorable cerebral hemodynamics and fastest resolution of intracranial hypertension.

Keywords

Pediatrics; traumatic brain injury; intracranial hypertension; fentanyl; hypertonic saline; pentobarbital

Introduction

Globally, traumatic brain injury (TBI) affects approximately 10 million people each year, is a leading cause of morbidity and mortality and is especially incident in childhood and adolescence(1). In children who remain comatose after TBI, death and unfavorable neurologic outcome are associated with intracranial hypertension(2-5). Monitoring of intracranial pressure (ICP) and treatment of intracranial hypertension have been mainstays of pediatric neurotrauma care for decades and have been a focus of evidenced-based guidelines(6). While data show acceptance of these guidelines - including prescription of sedatives/analgesics, hyperosmolar agents (hypertonic saline [HTS] and mannitol), and barbiturates for intracranial hypertension - the level of evidence within the literature that informs these recommendations is insufficient to standardize most aspects of care across centers(7-9).

When choosing therapies for life-threatening conditions, information regarding the efficacy of medications, including the rapidity of their effects, is necessary. In the case of therapies for intracranial hypertension, information is extremely limited. For children, the existing literature could not support Level I recommendations for any medication, and only a Level II recommendation for HTS and Level III evidence for pentobarbital were justified. No recommendations could be made for either opiates or mannitol. In total, these guidelines state (i) HTS “should be considered” and (ii) barbiturates “may be considered” for treatment of intracranial hypertension and are supported by data from only 45 children (6). The current study aims to improve upon this paucity of data supporting ICP-lowering agents in children with severe TBI.

Many believe that randomized controlled trials (RCTs) are necessary to determine superiority/inferiority of such agents. Currently, any potential RCT would be quite challenging - if not impossible - due to lack of equipoise for these agents, which have been in clinical use for decades despite limited evidence, and the difficulties in controlling for confounders(7). Such a study would not determine the rapidity of the effect of the medications unless all sites had the ability to capture data with sufficient granularity. An

innovative data collection method - one that integrates prospective collection of medication administration data and an automated, high-density database of continuous physiological variables from a single institution - could provide evidence suggesting the effectiveness of these therapies(10-12). Thus, this prospective study reports the effects of four commonly used therapies in the treatment of intracranial hypertension after severe TBI in children. We hypothesized that fentanyl, 3% HTS, mannitol, and pentobarbital would decrease ICP without significantly decreasing cerebral perfusion pressure (CPP).

Materials and Methods

This study was approved by the Institutional Review Board of the University of Pittsburgh and informed consent was obtained from the subject's parent(s) for medical record review. All children (< 18 years old) admitted between November 2011 and February 2013 with severe TBI (post-resuscitation Glasgow Coma Scale [GCS] score 8) who underwent ICP monitoring were prospectively enrolled in this study. Neurocritical care, including treatment of intracranial hypertension, was based on contemporary evidence-based guidelines and an institutional protocol described previously(13). Children were resuscitated based on Advanced Trauma Life Support guidelines. Children with a post-resuscitation GCS score 8 underwent neuromonitoring including an external ventricular drain (EVD) to continuously drain cerebrospinal fluid and an intraparenchymal ICP monitor (Codman, DePuy Orthopaedics, Warsaw, IN) to continuously monitor ICP, when feasible(10). Blood pressure was monitored using an arterial catheter. Intraparenchymal catheters were zeroed and calibrated based on the manufacturer's instructions. An externalized ventricular drain was zeroed at the tragus and the arterial catheter was zeroed at the phlebostatic axis (intersection of the 4th intercostal space and the mid-axillary line). A standard protocol for prevention of intracranial hypertension that is based on evidenced-based guidelines was initiated including continuous administration of fentanyl and a neuromuscular blocking agent, mild hyperventilation (target PaCO₂ 32 – 35 mm Hg), and continuous CSF diversion. All patients were cared for in a Pediatric Intensive Care Unit (PICU) by a dedicated Neurocritical Care team(14). All clinical decisions were made by the clinical team without consideration of inclusion in this study. In our routine practice, episodes of ICP 20 mm Hg for 5 min prompt treatment. Our typical practice sequentially uses fentanyl, hyperosmolar agents and pentobarbital (dosed to burst suppression), and subsequent treatment is often tailored to each individual patient. Benzodiazepines, propofol and dexmedetomidine are not routinely administered as sedatives or as therapies for intracranial hypertension. Data were collected for the entire duration of acute ICP monitoring.

An automated system for collection of vital signs, including ICP measurements and calculations of CPP (the arithmetic difference between the mean arterial blood pressure [from the arterial catheter] and the ICP) was employed in this study. Briefly, a data acquisition platform (Bedmaster EX, Excel Medical Electronics, Jupiter FL) was installed within the hospital network and time-stamped data (every 5 seconds) from the bedside monitor were captured for analysis. Bedside nurses or a study investigator prospectively recorded the precise time of administration of all ICP-related medications. Both the Bedmaster system and the medication data collectors used the time displayed on the patient monitor, thereby synchronizing the datasets. Intracranial hypertension episodes (ICP 20

mm Hg for > 5 min) that were treated with a study medication (fentanyl, HTS, mannitol, and pentobarbital) were identified for analysis. Episodes that the bedside nurse prospectively deemed to be induced by external stimuli (e.g., noise, endotracheal tube suctioning, etc.) were excluded, as were episodes that were treated with both a medication and adjustment of mechanical ventilator settings that increased minute ventilation. The electronic health record (EHR) was used to confirm the absence of changes in mechanical ventilation and to collect data related to use of concurrent therapies. The database was evaluated retrospectively for possible artifacts by both visual inspection of recorded waveforms and automated detection of extreme values of vital signs that were non-physiologic (e.g., MAP less than 0 or greater than 200 mm Hg). Confirmed artifacts were manually removed. Baseline ICP (or CPP) was defined as the mean value for the 5 minutes prior to initiation of the medication. Medication administrations missing baseline ICP data were excluded. Resolution of each intracranial hypertension crisis was defined as the time when ICP < 20 mm Hg for the subsequent 5 min. Treatment failure was defined as administration of a subsequent medication prior to resolution of the crisis.

Demographics, injury characteristics, cerebral hemodynamics, and concurrent therapies at the time of the medication were compared across medications with chi squared test (categorical variables) or analysis of variance (continuous variables). The ICP and CPP data were analyzed in several ways. To provide the most inclusive analysis of the effects of study medications, mean values of ICP and CPP were determined for epochs following the initiation of each bolus (0 – 5, 5 – 10, 10 – 15, 15 – 20, 20 – 25, 25 – 30, 30 – 45, 45 – 60, 60 – 90 and 90 – 120 minutes). Then, Kruskal-Wallis ANOVA with Dunn's test was used to compare each epoch vs. baseline (the 5 minutes prior to the initiation of the bolus [the duration that prompts guidelines-based therapy])(6). This analysis was repeated using the end of the bolus as time = 0 min. Next, to limit confounding due to multiple medications being administered for the same ICP crisis, data obtained after the administration of any subsequent medications were censored; mean values were recalculated; and epochs were again compared vs. baseline with Kruskal-Wallis ANOVA with Dunn's test. To further limit confounding by multiple medications, baseline values for ICP were compared to values measured 5min following initiation of the drug using a two-sample *t* test. In instances where a subsequent drug was given prior to the 5min time-point, the last value preceding the subsequent drug was carried forward and used as the 5min value, thereby removing any effect of subsequent drugs. Effects on ICP at 5min between drugs were then compared with mixed effect regression. This analysis was also performed using ICP data 5min after the conclusion of the drug. Baseline CPP was similarly compared vs. CPP at 5min after initiation of the drug, and also vs. CPP 5min after conclusion of the drug. Next, to control for the lack of independence between observations, the associations between medications and time to intracranial hypertension resolution (shown visually as a Kaplan-Meier curve) were analyzed with a frailty model that was adjusted for covariates that differed significantly between drug classes. Finally, the association of medication with treatment failure (prescription of a different medication prior to ICP crisis resolution) was assessed using a logistic mixed effects regression model. In the model, the independent variable was an indicator of medication and the dependent variable was the indication of treatment failure at five minutes. In each analysis, the significant *p* value was adjusted from 0.05 to account for

multiple comparisons (i.e. Bonferroni correction, Dunn's test). Data are presented as means (SEM) in mm Hg, unless otherwise specified.

Results

Twenty-five children were enrolled in this study (Table 1) and more than 2,700,000 individual time points (156.25 patient-days) were analyzed. Most children were male and blunt trauma was the most common mechanism of injury. Median post-resuscitation GCS score was 6 (range: 3 – 12). Three children had post-resuscitation GCS scores > 8 and then deteriorated to GCS score 8, thereby meeting inclusion criteria of the study. Seven children (28%) underwent decompressive surgery and 17 children (68%) survived to hospital discharge. Administration data for 362 doses of medications were recorded (fentanyl n = 242 doses; HTS n = 58; pentobarbital n = 55; mannitol n = 7). Six children received no medications for treatment of intracranial hypertension and three additional children received medications but all episodes were excluded based on the above criteria.

After applying exclusion criteria (stimulation: n = 94; ventilator manipulation: n = 79), 196 medication doses - administered to 16 children - were analyzed (median = 12 doses/patient [range = 1 – 26]). When baseline characteristics were compared across treatment groups (Table 2), fentanyl administration was associated with several variables: the diagnosis of abusive head trauma; younger patient age; milder magnitude of intracranial hypertension; and less frequent concurrent infusion of HTS, pentobarbital, or a neuromuscular blocking agent. Pentobarbital administration was associated with penetrating TBI and unfavorable GCS scores. Median drug administration durations were 1 min for fentanyl, 17 min for HTS and 20 min for pentobarbital.

In the most inclusive analysis, ICP was significantly decreased after administration of fentanyl, pentobarbital or HTS within 15-25 minutes of initiation of the bolus (Figure 1A) and within 15 minutes of the conclusion of the bolus (Figure 2A). CPP was not significantly decreased following any of the medications and was significantly increased following HTS boluses (Figures 1B & 2B). Findings were very similar after censoring epochs that were confounded by data following administration of subsequent medications (Figures 1C-D & 2C-D). Due to the limited number of evaluable doses of mannitol (n = 4), it was not included in this part of the analysis.

In the next analysis, HTS was associated with a significant improvement in ICP (mean change = -2.49 [0.80] mm Hg, p = 0.004) 5min after initiation of the medication (Figure 3a); this change differed significantly from the change in ICP after fentanyl (+0.53 [0.66] mm Hg, p = 0.004) by mixed effects modeling. At this time-point, CPP was augmented after HTS (+4.10 [1.38] mm Hg, p = 0.005) and compromised after fentanyl (-6.41 [0.82] mm Hg, p < 0.001). The change in CPP after fentanyl differed significantly (p < 0.001) from the changes in CPP after HTS and pentobarbital (+0.59 [0.75] mm Hg).

Five minutes following completion of the medication dose (Figure 3b), favorable effects on ICP were observed after HTS (-5.86 [1.58] mm Hg, p < 0.001) and pentobarbital (-5.29 [1.32] mm Hg, p < 0.001), both of which differed significantly from the change in ICP after

fentanyl ($p < 0.001$ for both). Again, CPP improved following HTS (+7.66 [2.08] mm Hg, $p = 0.001$) and deteriorated after fentanyl (-6.25 [0.86] mm Hg, $p < 0.001$). In post hoc testing, effects on CPP differed significantly amongst fentanyl, HTS, and pentobarbital (fentanyl vs. HTS: $p < 0.001$; fentanyl vs. pentobarbital: $p < 0.001$; HTS vs. pentobarbital: $p = 0.004$).

Time to ICP crisis resolution (Figure 4) differed significantly between drugs in the unadjusted ($p = 0.032$) and adjusted frailty models ($p = 0.031$). In the unadjusted model, HTS was associated with a greater than two-fold faster resolution of intracranial hypertension vs. pentobarbital (hazard ratio = 2.34 [1.183-4.628]). After adjusting for age, injury mechanism, GCS score, ICP and concurrent infusions (pentobarbital, HTS and neuromuscular antagonists), HTS was associated with a two-fold faster resolution of intracranial hypertension vs. both pentobarbital (HR = 2.171 [1.062-4.439]) and fentanyl (HR = 1.848 [1.086-3.155]). Time to resolution did not differ significantly between fentanyl and pentobarbital.

Rate of treatment failure differed significantly among drugs at all evaluated time-points between 15 min and 50 min following initiation of the medication (Table 3). In that time range, only fentanyl had a significantly increased odds ratio of treatment failure vs. reference (pentobarbital), with the 95% confidence interval not incorporating 1.00 at any time-point.

Discussion

In some circumstances, apparently simple questions remain unresolved for decades, leaving common medical practices without robust supporting evidence. Such is the case with the questions – which intracranial hypertension medication is most effective at resolving an ICP crisis and which works fastest? In our study using a data collection system time-linked to prospectively collected medication administration data, we provide the best evidence to date on the relative effectiveness of commonly used agents for this life-threatening condition in children with severe TBI. We found that HTS administration was associated with the most rapid resolution of intracranial hypertension and unique augmentation of CPP, while the salutary effects of pentobarbital on ICP are more gradual and lack concurrent CPP enhancement. Fentanyl was associated with decreased ICP, but was uniquely associated with acutely worsened CPP and the highest treatment failure rate.

Several different analytical techniques were employed in this study. We aimed to provide the most thorough description of ICP and CPP following the real-world administration of these medications to pediatric TBI subjects with intracranial hypertension, but we also aimed to maximally control for the confounding variables inherent in an observational study. The most inclusive and “descriptive” of these methods (Figures 1A-B & 2A-B) does not account for multiple medications per crisis or multiple crises per subject, but provides clinicians with the most comprehensive description of the time-course of the medications’ effects as used in clinical practice. Analyses shown in Figures 1C-D & 2C-D censored epochs that included data collected after treatment with another medication, thereby mitigating that confounder, but still treated all ICP crises as unique events. In a more

conservative analysis (Figure 3) designed to better control for the use of multiple medications, there were only sufficient data to analyze the effects of ICP and CPP at a single, hyper-acute time-point. Additionally, a frailty model was constructed to control for the inclusion of multiple ICP crises from individual subjects.

HTS has a long history of use in children, yet this is the first report of decreased ICP after HTS bolus therapy in children with intracranial hypertension after severe TBI. Fisher et al. previously reported that HTS (administered as a continuous infusion and compared to normotonic solutions) decreases ICP in children with TBI with a mean baseline ICP of 19 mm Hg, suggesting that the ICP-decreasing effect of HTS is not exclusive to intracranial hypertension(15). This single report with 18 children formed the basis for a Level II recommendation in the current evidenced-based guidelines (6). In our study, we confirm that HTS was effective at decreasing ICP but add to the literature that it was associated with the fastest resolution of intracranial hypertension compared to other therapies that were evaluated. Our data suggest that HTS may be preferable to other agents for this purpose. Assessment of the effect of therapies on the timing of resolution of such crises is lacking in the literature. Rapid resolution of ICP crises might be extremely important given recent work suggesting detrimental effects of even brief episodes of intracranial hypertension(16). This novel finding sets the stage for additional investigation and confirmation. Importantly, our study design – particularly the fact that initiation of the medication defined the “start” of the intervention – biased against these findings since rapidly infused medications (fentanyl and mannitol) would theoretically have more time to demonstrate effects than those that were administered less rapidly (HTS and pentobarbital). Regardless, HTS was associated with more rapid intracranial hypertension resolution than either fentanyl or pentobarbital.

Importantly, HTS was also the only medication studied associated with increased CPP. Within the neurotrauma community, significant debate continues regarding the relative importance of intracranial hypertension and cerebral perfusion pressure. However, our data suggest that HTS might be the preferred agent for both measures. As a volume expander, HTS likely increases blood pressure while avoiding the vasodilatory or negative inotropic effects of the other tested agents. Overall, our findings are consistent with a recent meta-analysis suggesting superiority of HTS versus mannitol to reduce ICP in adults and children in neurocritical care, though confirmatory studies including additional mannitol data are needed (17). Additionally, we recognize that some data support that intracranial hypertension worsens outcome independent of CPP, so the ICP-lowering effects we observed with other drugs may be beneficial as well(18).

Opioids and barbiturates are commonly administered to children with severe TBI, yet only a single study pertaining to ICP met the criteria for inclusion into the recently published guidelines(19). Both fentanyl and pentobarbital were associated with a gradual decrease in ICP in our study. Neither fentanyl nor pentobarbital was associated with a significant improvement in ICP 5 min after medication initiation, but pentobarbital was associated with a significant decrease in ICP 5 min following medication completion. This supports two prior reports of resolution of ICP crises following pentobarbital administration in some children, though our data additionally inform practitioners that ICP reduction may be gradual(19, 20). This differs from the more immediate ICP reduction observed with HTS

and may be clinically relevant. Interestingly, pentobarbital was not associated with decreased CPP at either time-point, supporting that the cardiovascular depressant effects of pentobarbital can be mitigated.

Our data suggest a limited role for fentanyl for treatment of intracranial hypertension. Overall, ICP was decreased following fentanyl administration. However, Fentanyl was associated with the highest treatment failure rate, and unfavorable findings (decreased CPP and unchanged ICP) 5min after administration. This differs from prior studies in adults with TBI which showed fentanyl is associated with decreased blood pressure and increased ICP, presumably due to hypotension-induced cerebral vasodilation and increased cerebral blood volume (CBV)(21, 22). That ICP did not increase with decreased CPP in our cohort suggests altered autoregulation and/or a concomitant decrease in CBV by a secondary mechanism, possibly decreased cerebral metabolic rate(23, 24). This mechanism could explain the decreased ICP observed after fentanyl and why fentanyl monotherapy was associated with resolution of intracranial hypertension in select instances. Similar to pentobarbital, ICP-lowering effects of fentanyl appear gradual. Pending further study, clinicians must weigh the risks of CPP decrements and treatment failure against any ICP-decreasing benefits of fentanyl.

We believe our study has several strengths. The size of this cohort is similar to (or larger than) those of several therapeutic studies cited in the most recent expert guidelines(15, 19, 25-28). Collecting data near-continuously uniquely strengthened our study by increasing the volume and precision of our data while objectively determining unbiased periods of intracranial hypertension(10). All ICP crises prompted by noxious stimuli or treated with mechanical ventilator adjustment were identified and excluded – mitigating potential biases in the data. In fact, this may have prejudiced our findings against fentanyl since the analgesic effects may have had substantial benefits following noxious stimuli; our study should not be interpreted as evidence against the use analgesics or sedatives in children with severe TBI in this setting. Lastly, our system identified episodes that were treated with multiple medications, so that confounded data could be censored from the analysis. As a result, we have an extensive assessment on the effect of these medications on intracranial hypertension in children with severe TBI.

Our study has several limitations. As with all observational studies, causality between medication administration and event resolution cannot be definitively determined. We used many techniques to decrease possible bias within our observation. Such techniques restricted some analyses to hyper-acute time-points, but we also provided a descriptive analysis of more delayed time-points. While ICP measurements from intraparenchymal and EVD monitors correlate nearly perfectly, small differences in ICP values (~3 mm Hg) may exist(10). However, we controlled for this by using the same monitoring device to measure ICP both before and after each study medication dose. This paired analysis mitigated differences in monitoring techniques. Our study was performed within our clinical center, and all subjects were treated using the same clinical protocol. It is likely that our protocol (such as our medication dosing ranges, universal administration of neuromuscular blocking agents, avoidance of benzodiazepines, and other factors) may interact with the effectiveness of the medications administered. Therefore, our data need to be confirmed by others using

contemporary protocols before definitive conclusions should be accepted. However, it is unclear to us how another study design, such as a randomized controlled trial, could fully answer the questions that we posited. Without a data collection system in place similar to ours, a traditional RCT would not be able to answer the temporal questions posed by our study. Importantly, our data did not address long-term functional outcome. However, our data does address a major gap in the guidelines regarding acute medication effects and provide novel information that can serve as the basis for future studies targeting long-term outcomes. Scant data for mannitol were collected because of our clinical practice, which is another limitation to our study. Our two outcome variables, ICP and CPP, are mathematically coupled, which may lead to statistical interactions. However, ICP and CPP are the two variables to which guidelines-based therapies are targeted, while MAP is not (even though it is directly measured). Lastly, our study could not analyze the effects of continuous infusions of fentanyl, HTS and pentobarbital. It is possible that continuous therapy may decrease the effectiveness of bolus medications through a number of possible mechanisms - quantity of available binding sites for opiates and barbiturates, degree of hypernatremia for HTS, physiological tolerance for narcotics, or others. Further study of a larger cohort could investigate whether continuous infusions (or other pre-treatment variables, such as serum sodium, electroencephalogram characteristics and time after injury) are associated with differences in bolus therapy effectiveness.

Conclusions

In conclusion, ICP was decreased after administration of fentanyl, HTS and pentobarbital. HTS may warrant consideration as the first-line drug for treating intracranial hypertension in such children, as it was associated with the most favorable cerebral hemodynamics and fastest resolution of intracranial hypertension. Pending further description of delayed ICP attenuation, judicious use of fentanyl is suggested for ICP crises due to the possibility of CPP reduction and frequent failure rate.

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Figure 1. ICP and CPP before and after initiation of ICP-directed therapy

For each medication administration, mean ICP and CPP (mm Hg) were calculated for each epoch relative to initiation of the bolus. Error bars denote interquartile range. Asterisks denote median values significantly different than the 5 minutes preceding initiation of the bolus by Kruskal-Wallis ANOVA with Dunn's test. Figures A and B include all epochs. Epochs confounded by administration of the subsequent medication were censored from Figures C and D.

Figure 2. ICP and CPP before and after conclusion of ICP-directed therapy

For each medication administration, mean ICP and CPP (mm Hg) were calculated for each epoch relative to conclusion of the bolus. Error bars denote interquartile range. Asterisks denote median values significantly different than the 5 minutes preceding initiation of the bolus by Kruskal-Wallis ANOVA with Dunn's test. Figures A and B include all epochs. Epochs confounded by administration of the subsequent medication were censored from Figures C and D.

Figure 3. Changes in ICP and CPP from baseline to 5min after the medication

The boxes represent the mean difference between the baseline value and the value 5min after the medication. Error bars represent standard error of the mean. Changes in ICP (shaded boxes) are plotted on the left y-axis (with negative values above the x-axis). Changes in CPP (open boxes) are plotted on the right y-axis. Asterisks indicate mean differences that are significantly different than zero ($p < 0.05$). Figure 3a shows data relative to initiation of the medication; Figure 3b shows data relative to completion of the medication.

Figure 4. Kaplan-Meier curve showing time until resolution of the intracranial hypertension episode

This is a visual representation of the time to ICP crisis resolution for each treatment group. Resolution was defined as ICP < 20 mm Hg for the subsequent 5 minutes.

Table 1**Baseline characteristics**

Characteristics of all children and children whom received medications that were included in the analyses.

	All patients	Subset given analyzed boluses
Number of patients	25	16
Age (months)	64 (34 – 168)	44 (34 – 124)
Male	21 (84%)	12 (75%)
Mechanism		
Blunt	17 (68%)	9 (56%)
AHT	4 (16%)	3 (19%)
GSW/Penetrating	4 (16%)	4 (25%)
GCS score *	5 (3 - 7)	5 (3 - 7)
PRISM score	18 (12 – 22)	19 (12 – 23)
Continuous Infusions		
HTS	19 (76%)	14 (88%)
Penobarbital	7 (28%)	6 (38%)
Vecuronium/Cisatracurium	25 (100%)	16 (100%)
Surgical Decompression	7 (28%)	6 (38%)
Survival to Discharge	17 (68%)	13 (81%)

Data are n (%) or median (interquartile range). AHT=abusive head trauma. GSW=gun shot wound. GCS=Glasgow Coma Scale. PRISM=Pediatric Risk of Mortality. HTS=hypertonic saline. ICP=intracranial pressure.

* prior to ICP monitoring

Table 2
Characteristics by drug class

Patient characteristics at the time of medication administration for all boluses included in the analyses.

	Fentanyl	HTS	Pentobarbital	p value
Boluses included in analyses	112	41	39	
Bolus dose	2 (2 - 3) ug/kg	3 (2 - 5) ml/kg	5 (2.25 - 5) mg/kg	
Bolus duration (minutes)	1 (1 - 1)	17 (10 - 21.5)	20 (15 - 30)	
Age (months)	43.5 (34 - 109)	102 (43 - 168)	102 (34 - 168)	0.044
Male	84 (75.0%)	27 (65.9%)	28 (71.8%)	0.531
Mechanism of Injury				0.02
Blunt	61 (54.5%)	27 (65.9%)	17 (43.6%)	
AHT	15 (13.4%)	1 (2.4%)	1 (2.6%)	
GSW/Penetrating	36 (32.1%)	13 (31.7%)	21 (53.9%)	
GCS score[*] (median [range])	5 (3 - 7)	5 (3 - 7)	3 (3 - 3)	<0.001
Concurrent Continuous Infusions				
HTS	64 (57.1%)	31 (75.6%)	35 (89.7%)	<0.001
Pentobarbital	13 (11.6%)	11 (26.8%)	25 (64.1%)	<0.001
Vecuronium/Cisatracurium	101 (90.2%)	41 (100%)	39 (100%)	0.013
Preceded by Surgical Decompression	24 (21.4%)	12 (29.3%)	11 (28.2%)	0.505
Hours after Admission	56 (27 - 82)	43 (16 - 91)	70 (48 - 103)	0.259
ICP prior to Rx (mm Hg) (mean [SD])	21.7 (5.4)	23.9 (5.9)	24.3 (5.8)	<0.001
CPP prior to Rx (mm Hg) (mean [SD])	66.6 (13.2)	64.1 (14.1)	64.3 (10.7)	0.421

Data are n (%) or median (IQR) unless otherwise noted. Groups compared with chi squared test or Kruskal-Wallis ANOVA. AHT=abusive head trauma. GSW=gun shot wound. GCS=Glasgow Coma Scale. HTS=hypertonic saline. ICP=intracranial pressure. CPP=cerebral perfusion pressure.

* prior to ICP monitoring

Table 3**Odds of Treatment Failure**

The odds of treatment failure, defined as administration of another ICP-directed therapy prior to resolution of the ICP crisis, are shown for various time-points relative to initiation of the study medication.

Minutes after start of bolus	Fentanyl	HTS	Mannitol	Pentobarbital	<i>p</i> value for timepoint
5	1.06 (0.94 - 1.19)	1.00 (0.87 - 1.14)	1.19 (0.86 - 1.64)	reference	0.502
10	1.14 (0.99 - 1.31)	0.97 (0.82 - 1.15)	1.13 (0.75 - 1.69)	reference	0.122
15	1.24 (1.06 - 1.44)*	0.99 (0.83 - 1.19)	1.13 (0.73 - 1.74)	reference	0.021
20	1.36 (1.15 - 1.62)*	1.00 (0.82 - 1.23)	1.08 (0.68 - 1.72)	reference	0.002
25	1.47 (1.23 - 1.76)*	1.04 (0.85 - 1.28)	1.10 (0.69 - 1.76)	reference	< 0.001
30	1.41 (1.17 - 1.69)*	1.01 (0.82 - 1.25)	1.03 (0.64 - 1.66)	reference	0.001
35	1.34 (1.12 - 1.62)*	1.05 (0.85 - 1.30)	0.97 (0.59 - 1.60)	reference	0.011
40	1.35 (1.12 - 1.63)*	1.08 (0.87 - 1.34)	0.96 (0.58 - 1.57)	reference	0.012
45	1.36 (1.13 - 1.64)*	1.17 (0.94 - 1.45)	0.96 (0.58 - 1.58)	reference	0.021
50	1.13 (1.09 - 1.57)*	1.11 (0.89 - 1.38)	0.91 (0.55 - 1.50)	reference	0.035
55	1.29 (1.07 - 1.55)	1.11 (0.89 - 1.39)	0.89 (0.54 - 1.46)	reference	0.051
60	1.28 (1.06 - 1.54)	1.08 (0.87 - 1.35)	1.10 (0.66 - 1.81)	reference	0.079
65	1.22 (1.01 - 1.48)	1.03 (0.83 - 1.28)	1.05 (0.64 - 1.74)	reference	0.131
70	1.19 (0.99 - 1.44)	1.01 (0.81 - 1.25)	1.03 (0.62 - 1.70)	reference	0.172
75	1.19 (0.99 - 1.44)	1.01 (0.81 - 1.25)	1.03 (0.62 - 1.70)	reference	0.172
80	1.19 (0.99 - 1.44)	1.01 (0.81 - 1.25)	1.03 (0.62 - 1.70)	reference	0.172
85	1.15 (0.96 - 1.39)	1.00 (0.80 - 1.25)	1.00 (0.61 - 1.66)	reference	0.309
90	1.14 (0.95 - 1.38)	0.98 (0.78 - 1.22)	0.98 (0.60 - 1.62)	reference	0.290
95	1.12 (0.92 - 1.35)	0.96 (0.77 - 1.19)	0.96 (0.58 - 1.59)	reference	0.331
100	1.12 (0.92 - 1.35)	0.96 (0.77 - 1.19)	0.96 (0.58 - 1.59)	reference	0.331
105	1.11 (0.92 - 1.34)	0.93 (0.75 - 1.16)	0.94 (0.57 - 1.54)	reference	0.259
110	1.11 (0.92 - 1.34)	0.93 (0.75 - 1.16)	0.94 (0.57 - 1.54)	reference	0.245
115	1.08 (0.90 - 1.31)	0.93 (0.75 - 1.16)	1.18 (0.72 - 1.93)	reference	0.350
120	1.11 (0.92 - 1.33)	0.96 (0.77 - 1.19)	1.20 (0.73 - 1.95)	reference	0.351

Odds differed significantly between medications at 15 – 50min. At each of those time-points, only Fentanyl had significantly higher odds of treatment failure vs. reference in *post-hoc* analysis.

* $p < 0.005$ for that drug vs. pentobarbital