

# Osmolar therapy in pediatric traumatic brain injury\*

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**Objectives:** To describe patterns of use for mannitol and hypertonic saline in children with traumatic brain injury, to evaluate any potential associations between hypertonic saline and mannitol use and patient demographic, injury, and treatment hospital characteristics, and to determine whether the 2003 guidelines for severe pediatric traumatic brain injury impacted clinical practice regarding osmolar therapy.

**Design:** Retrospective cohort study.

**Setting:** Pediatric Health Information System database, January, 2001 to December, 2008.

**Patients:** Children (age <18 yrs) with traumatic brain injury and head/neck Abbreviated Injury Scale score  $\geq 3$  who received mechanical ventilation and intensive care.

**Interventions:** None.

**Measurements and Main Results:** The primary outcome was hospital billing for parenteral hypertonic saline and mannitol use, by day of service. Overall, 33% (2,069 of 6,238) of the patients received hypertonic saline, and 40% (2,500 of 6,238) received mannitol. Of the 1,854 patients who received hypertonic saline or

mannitol for  $\geq 2$  days in the first week of therapy, 29% did not have intracranial pressure monitoring. After adjustment for hospital-level variation, primary insurance payer, and overall injury severity, use of both drugs was independently associated with older patient age, intracranial hemorrhage (other than epidural), skull fracture, and higher head/neck injury severity. Hypertonic saline use increased and mannitol use decreased with publication of the 2003 guidelines, and these trends continued through 2008.

**Conclusions:** Hypertonic saline and mannitol are used less in infants than in older children. The patient-level and hospital-level variation in osmolar therapy use and the substantial amount of sustained osmolar therapy without intracranial pressure monitoring suggest opportunities to improve the quality of pediatric traumatic brain injury care. With limited high-quality evidence available, published expert guidelines appear to significantly impact clinical practice in this area. (Crit Care Med 2012; 40: 208–215)

**KEY WORDS:** brain edema; craniocerebral trauma; hypertonic saline solution; intracranial hypertension; mannitol; pediatrics

Pediatric traumatic brain injury (TBI) is an important public health problem in the United States, and is estimated to cause approximately 2,300 deaths, 42,000 hospitalizations, and 404,000 emergency department visits annually among children 0–14 yrs old (1, 2). TBI also causes substantial and long-lasting disability in children (3). Elevated intracranial pressure (ICP)/intracranial hypertension develops after TBI via several mechanisms, including cellular swelling and blood-brain barrier disruption (4).

The July, 2003 guidelines for the management of severe pediatric TBI support the use of mannitol and/or hypertonic saline (any concentration >0.9% saline) to decrease ICP at the discretion of the treating physician, but neither osmolar agent has sufficient evidence for a higher-grade recommendation (5, 6). Both broad clinical use and published studies support mannitol use in adult TBI patients with intracranial hypertension, but its pediatric use as of 2003 was supported by only two single-center retrospective analyses (6–10). Use of hypertonic saline as a therapy for elevated ICP was supported by three prospective pediatric studies (11–14). Choice of osmolar agent to treat intracranial hypertension and variation in care across patient and hospital characteristics has not been evaluated.

The purpose of this study was to describe patterns of mannitol and hypertonic saline use in children with TBI, to evaluate any potential associations of preferential mannitol and hypertonic saline use with demographic, injury type, injury severity, or treatment hospital characteristics, and to assess change in use after publication of the 2003 guide-

lines. Because of pediatric-specific studies supporting hypertonic saline, we hypothesized that, after adjustment for clustering by hospital and baseline trend, hypertonic saline use would increase after the guidelines were published.

## METHODS

### Study Design

We conducted a retrospective cohort study of the Pediatric Health Information System (PHIS) database developed by the Child Health Corporation of America (15) (Shawnee Mission, KS). We studied children who received care for TBI, including intensive care unit (ICU) admission and mechanical ventilation, at a PHIS hospital.

### Setting

Child Health Corporation of America is a collaboration of >40 children's hospitals, and PHIS contains administrative data, including demographics, diagnoses, procedures, and charges. In addition, a subset of PHIS hospitals submits "Level II" data, including pharmacy, clinical services, imaging, and supply data (16). As described by Conway and Keren

\*See also p. 336.

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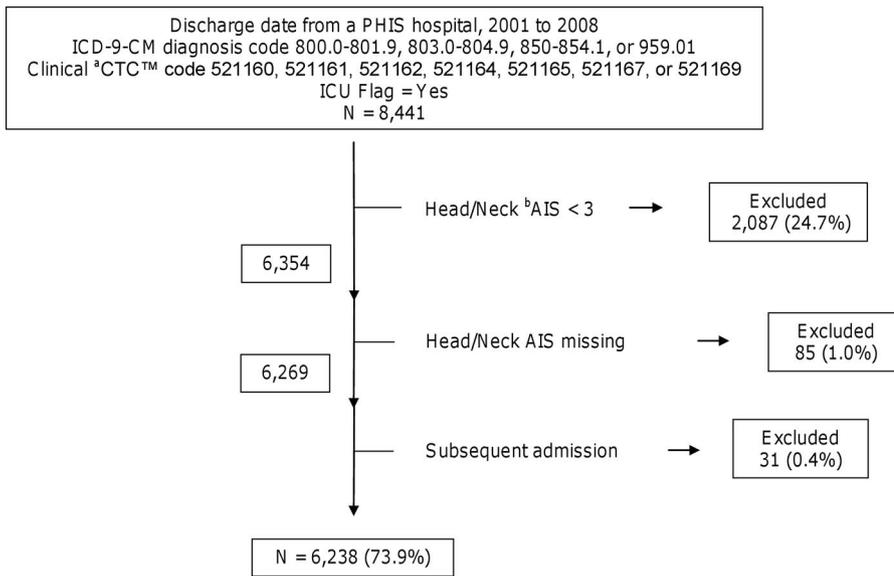
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<sup>a</sup>Clinical Transaction Classification™

<sup>b</sup>Maximum Abbreviated Injury Scale for Head/Neck body region, derived from ICD-9-CM diagnosis codes using ICDMAP-90

Figure 1. Patient selection method for children <18 yrs old with traumatic brain injury. PHIS, Pediatric Health Information System database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CTC, clinical transaction classification; ICU, intensive care unit; AIS, Abbreviated Injury Scale; ICDMAP-90, software used to calculate AIS and ISS scores.

(17): “[o]versight of PHIS data quality and accuracy is a joint effort between Child Health Corporation of America, Thomson Healthcare (the data manager), and participating hospitals. Data are de-identified at the time of data submission and subjected to 175 reliability and validity checks. Data are accepted into the database when classified errors occur in <2% of a hospital’s quarterly data.” We obtained data from PHIS regarding patients admitted to the 26 hospitals submitting “Level II” data with patients that met our inclusion criteria. Our data use agreement prevents identification of hospitals, but inpatient data on many PHIS hospitals have been published previously (16).

## Selection of Participants

We identified children <18 yrs of age treated at a PHIS hospital with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnosis code for TBI (800.0–801.9, 803.0–804.9, 850–854.1, or 959.01) and clinical coding for mechanical ventilation and ICU care (see below) from January, 2001 to December, 2008 (Fig. 1). These ICD-9-CM diagnosis codes are used by the Centers for Disease Control to track hospitalization and emergency department visits for TBI rates nationally (18). Mechanical ventilation was identified using clinical transaction classification codes 521160, 521161, 521162, 521164, 521165, 521166, 521167, or 521169 (19). Clinical transaction classification codes reflect hospital

billing, and can be used to identify services received by patients (16, 17, 20). ICU care was identified using an “ICU Flag” coded by PHIS.

We calculated injury severity score (ISS, or specifically, ICD/ISS) and maximum abbreviated injury scale (AIS) body region scores from ICD-9-CM diagnosis codes using ICDMAP-90 software (Johns Hopkins University and Tri-Analytics, Baltimore, MD) (21). We chose maximum AIS scores by ISS body region (six regions). To select for patients with severe TBI, we excluded patients with maximum head/neck body region AIS scores of <3 (“serious”) and the few patients with missing head/neck AIS scores (Fig. 1). In addition, we excluded subsequent admissions.

## Methods and Measurements/ Outcome Measures

We analyzed the study population by demographic characteristics, insurance status, injury characteristics and severity, and admission date. We dichotomized admission date at July, 2003, when the guidelines were published (5). We also analyzed the patients by hospital American College of Surgeons (ACS) Pediatric Trauma designation (22) and percent of study patients with a government primary payer.

The primary outcomes of interest were pharmacy billing (clinical transaction classification) codes for parenteral hypertonic saline or mannitol. Each drug has an associated “day

of service” code indicating the hospital day on which that drug was ordered. Hypertonic saline and mannitol may be used only rarely to treat imminent herniation, intermittently to treat intracranial hypertension, or as part of a treatment strategy to minimize ICP (6). To identify patients given osmolar therapy as a treatment strategy, we selected patients who received hypertonic saline or mannitol for at least 2 days during the first week after hospital admission. In all analyses, we determined the proportion of patients who received a particular drug for x or more days, using only those patients who had a length of stay of at least x days.

To evaluate other indications for hypertonic saline, we identified patients with a diagnosis of hyponatremia using ICD-9-CM diagnosis code 276.1.

## Primary Data Analyses

We compared hypertonic saline and mannitol use across categories defined by patient and hospital variables using the chi-square test.

We used interrupted time series analyses to assess whether the July, 2003 guidelines were associated with changes in the use of hypertonic saline and mannitol. We built segmented multivariate linear regression models with separate terms for the baseline trend, the change in level with guideline publication, and the change in trend after guideline publication. We suspected *a priori* that substantial variation in hypertonic saline and mannitol use between hospitals existed, and used robust standard errors adjusted for clustering by hospital. We excluded July–December, 2003 from the time series analyses (these patients remained in the dataset for all other analyses) as a lag period to allow for uptake of the new guidelines (23). We built a similar model for changes in the diagnosis of hyponatremia over time. Model fit and autocorrelation were assessed using visual inspection of model residuals.

We used multivariate logistic regression models with clustering by hospital, an exchangeable correlation structure, and robust standard errors calculated using generalized estimating equations (GEE) to estimate the effect of candidate predictors on osmolar therapy use. Variables with bivariate associations with hypertonic saline or mannitol use were candidates for inclusion, and we parameterized the variables to maximize clinical interpretability. Because an ICP monitor is required for ICP-directed therapy, we did not include the presence of an ICP monitor in the GEE models.

We used random-effects logistic regression (16, 17) and the intraclass correlation coefficient to quantify variation in mannitol and hypertonic saline use between hospitals. Those variables identified in the GEE models

as having independent associations with osmolar therapy use were included as covariates.

We defined statistical significance as  $p < .05$  in all analyses. Statistical analyses were performed using Intercooled STATA, version 10 (StataCorp, College Station, TX). The Institutional Review Board at the University of the Utah School of Medicine waived the need for approval.

## RESULTS

### Characteristics of Study Subjects

We identified 8,441 patients in the PHIS database and 6,238 remained in the dataset after exclusions (Fig. 1). In each study month, a median of 64 (interquartile range 53–76) patients were discharged from 26 PHIS hospitals. In-hospital mortality was 18.8% (1,173 of 6,212), and 26 patients (0.42%) were missing disposition data.

Most patients were male, white, and had government-funded insurance (Table 1). Infants (<1 yr of age) accounted for 20% of the patients. Most patients (71%) had an intracranial hemorrhage (ICH), and 55% had a skull fracture. The median ISS score was 16 (interquartile range 10–25). Most of the hospitals did not have an ACS Pediatric Trauma designation (22). The median number of study participants per hospital was 221 (range 34–557, interquartile range 133–363). All 26 hospitals submitted data both before and after 2003. Approximately two-thirds of the patients were admitted after the July, 2003 guidelines were published.

### Main Results

Overall, 33% (2,069 of 6,238) of the patients received hypertonic saline and 40% (2,500 of 6,238) received mannitol, with 22% (1,347 of 6,238) receiving both, 18% (1,153 of 6,238) only mannitol, and 12% (722 of 6,238) only hypertonic saline. Approximately 26% of all patients received 3% saline, 13% received 10%–25% saline, and <1% received 5% saline (several patients received multiple concentrations, not shown). Osmolar therapy use was substantial on the first day of admission and peaked on the second day of admission (Fig. 2). Mannitol use decreased throughout the first week of therapy, but hypertonic saline administration continued at a fairly constant rate. Of those patients still hospitalized on the 7<sup>th</sup>

**Table 1.** Patient and hospital characteristics of pediatric traumatic brain injury cohort

Patients and Hospital Characteristics	Patients, n (%) n = 6238
Age	
0 to 364 days	1273 (20)
1 to <5 yrs	1603 (26)
5 to <13 yrs	2177 (35)
13 to <18 yrs	1185 (19)
Gender	
Female	2239 (36)
Male	3996 (64)
Missing	3 (0)
Race	
White	3858 (62)
Black	1467 (24)
Other	607 (10)
Missing	306 (5)
Insurance status	
Government	2964 (48)
Private	1944 (31)
Other	368 (6)
Missing	962 (15)
Admission date	
2000–7/2003	2194 (35)
8/2003–2008	4044 (65)
Injuries	
Any intracranial hemorrhage	4449 (71)
Any skull fracture	3429 (55)
Intracranial pressure monitor	
No	3967 (64)
Yes	2271 (36)
Head/neck abbreviated injury scale score <sup>a</sup>	
3 (Serious)	3055 (49)
4 (Severe)	1949 (31)
5 (Critical)	1227 (20)
6 (Unsurvivable)	7 (0)
Injury severity score	
<15	2313 (37)
≥15	3925 (63)
American college of surgeons pediatric trauma level designation (# hospitals) <sup>b</sup>	
I (n = 8)	2024 (32)
II (n = 2)	534 (9)
None (n = 16)	3680 (59)
% Government payer <sup>c</sup>	
15–49.9%	3209 (51)
50–76%	3029 (49)

Column percentages may not add to 100 because of rounding.

<sup>a</sup>Abbreviated Injury Scale score, head/neck body region, derived using ICDMAP-90; <sup>b</sup>injury Severity score, as derived from diagnosis codes using ICDMAP-90; <sup>c</sup>by hospital, number of patients in this cohort with a government plan as the primary payer.

day after admission, approximately 27% of those who had received any hypertonic saline and 16% of those who had received any mannitol were still receiving those agents.

Almost 5% of patients (4.6%) had a diagnosis of hyponatremia. Hypertonic saline use for ≥2 days was more common

in patients with hyponatremia than without hyponatremia (43.4% vs. 18.4%,  $p < .001$ ). There was no gender difference in the diagnosis of hyponatremia (5.0% girls vs. 4.4% boys,  $p = .590$ ).

### Bivariate Analyses

Use of osmolar therapy for ≥2 days in the first week showed statistically significant differences across age groups and insurance status, with older children and those with commercial insurance receiving more osmolar agents (not shown). Patients cared for at ACS Level I hospitals and hospitals without an ACS designation were more likely to receive osmolar therapy for ≥2 days in the first week than those cared for at ACS Level II hospitals (Table 2).

Children with any ICH or any skull fracture received more osmolar therapy than children without those injuries (Table 2). Children with recorded epidural hemorrhage (EDH) without skull fracture tended to receive mannitol for one day (41%, not shown), but few received hypertonic saline or mannitol for 2 days in the first week (13% and 11%, respectively, Table 2). Both hypertonic saline and mannitol use increased with increasing head/neck injury severity (AIS) and overall injury severity (ISS). Children with ICP monitoring were more likely to receive both hypertonic saline and mannitol (Table 2). Of the 1,854 children who received ≥2 days of hypertonic saline (650 patients), mannitol (663), or both (541), 543 (29%) did not have an ICP monitor (not shown). Of the 372 infants who received ≥2 days of osmolar therapy, 192 (52%) did not have an ICP monitor.

### Interrupted Time Series Analyses

Using segmented multivariate linear regression, excluding patients admitted July–December, 2003, and adjusting for clustering by hospital, we found that hypertonic saline use was increasing slowly and mannitol use was increasing fairly quickly before the guidelines were published (Fig. 3 and Table 3). Following guideline publication, hypertonic saline use increased and mannitol use decreased substantially. Thereafter, hypertonic saline use continued to increase and mannitol use continued to decrease. Each of the predictors (baseline trend, change with guidelines, and postguidelines

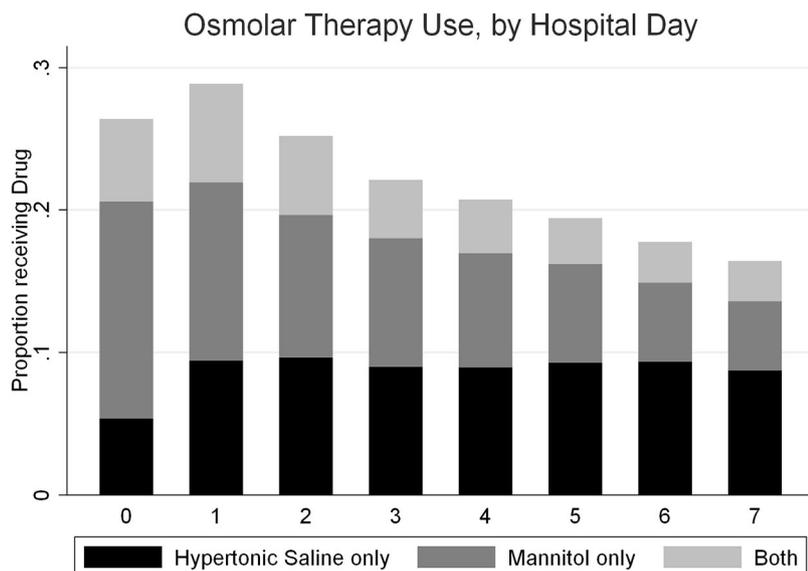


Figure 2. Hypertonic saline and mannitol use, by hospital day.

Table 2. Hypertonic saline or mannitol use for  $\geq 2$  days ( $n = 6093$  with length of stay  $\geq 2$  days), by hospital and injury characteristics and intracranial pressure monitoring

Hospital and Injury Characteristics	Hypertonic Saline, n (Row%) n = 1191 of 6093	$\chi^2$ p	Mannitol, n (Row%) n = 1204 of 6093	$\chi^2$ p
Hospital american college of surgeons, pediatric trauma level		<.001		<.001
I (n = 1983)	388 (20)		454 (23)	
II (n = 520)	59 (11)		84 (16)	
None (n = 3590)	744 (21)		666 (19)	
Injury type				
Any intracranial hemorrhage vs. none (n = 4347)	931 (21)	<.001	936 (22)	<.001
Any skull fracture vs. none (n = 3350)	695 (21)	.009	707 (21)	.004
Epidural hematoma, <sup>a</sup> no fracture (n = 220)	28 (13)	.009	24 (11)	.001
Subarachnoid hemorrhage, <sup>b</sup> no fracture (n = 536)	102 (19)	.752	100 (19)	.502
Subdural hemorrhage, <sup>c</sup> no fracture (n = 1232)	238 (19)	.821	273 (22)	.018
Head/neck abbreviated injury scale score <sup>d</sup>		<.001		<.001
3 (n = 3040)	532 (18)		521 (17)	
4 (n = 1931)	385 (20)		369 (19)	
5-6 (n = 1122)	274 (24)		314 (28)	
Injury severity score <sup>e</sup>		<.001		<.001
<15 (n = 2302)	389 (17)		401 (17)	
$\geq 15$ (n = 3791)	802 (21)		803 (21)	
Intracranial pressure monitor		<.001		<.001
Yes (n = 2248)	893 (40)		899 (40)	
No (n = 3845)	298 (8)		305 (8)	

<sup>a</sup>Epidural hematoma without skull fracture (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis codes 852.4 and 852.5); <sup>b</sup>subarachnoid hemorrhage without skull fracture (ICD-9-CM diagnosis codes 852.0 and 852.1); <sup>c</sup>subdural hemorrhage without skull fracture (ICD-9-CM diagnosis codes 852.2 and 852.3); <sup>d</sup>abbreviated Injury Scale score, head/neck body region, derived using ICDMAP-90; <sup>e</sup>injury Severity score, derived using ICDMAP-90.

change in trend) was independently associated with osmolar agent use in each model.

A similar model for the diagnosis of hyponatremia had a baseline rate of 2.3% of patients and was slowly increasing (0.07% per month,  $p < .001$ ) before the guidelines, increased 0.6% with

the guidelines ( $p = .001$ ), and slowly decreased thereafter ( $-0.06\%$  per month,  $p < .001$ ), with little net change from the beginning to the end of the study.

Visual inspection of residuals for the hypertonic saline and mannitol time series models suggested a good fit and

no significant autocorrelation (not shown).

## GEE Models

Using multivariate logistic regression models with clustering by hospital, exchangeable correlation structure, and robust standard errors calculated using generalized estimating equations, we found that older age, admission after July, 2003, any ICH, any skull fracture, SDH (mannitol only), and higher head/neck AIS score were independently associated with hypertonic saline and mannitol use for  $\geq 2$  days in the first week (Table 4). As expected, children with EDH were less likely to receive osmolar therapy for  $\geq 2$  days. Government primary insurance payer and ISS were significant in the bivariate analyses but not in the multivariate models. In an exploratory fashion, we added an interaction term between SDH and age to the mannitol model, and it was not statistically significant. ACS Trauma designation, although significant in the bivariate analyses, is a parameterization of treatment hospital and is the cluster variable in the GEE models.

## Random-Effects Models

Using random-effects logistic regression adjusted for clustering by hospital and the independent predictors from the GEE models (age, any ICH, any skull fracture, no EDH [both], SDH [mannitol only], AIS, and admission after July, 2003), we estimated from the intraclass correlation coefficient that 12.2% (95% confidence interval 7.0% to 20.4%) of the variance in hypertonic saline use for  $\geq 2$  days in the first week was between-hospital variance. In a similar fashion, we estimated that 14.8% (95% confidence interval 8.4% to 24.7%) of the variance in mannitol use for  $\geq 2$  days in the first week was between-hospital variance.

## Sensitivity Analyses

Because the insurance payer variable had missing data, which necessarily excluded those records from the logistic GEE models, we constructed otherwise identical models without a payer term and obtained similar point estimates and precision for the other predictors (not shown).

Our patient selection criteria reliably identified acute rather than rehabilitative

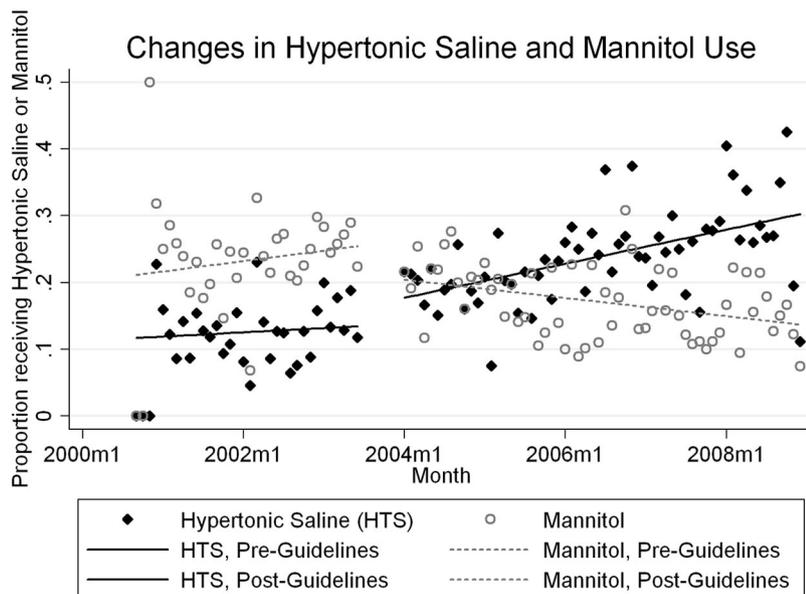


Figure 3. Changes in the proportion of children given hypertonic saline (HTS) and mannitol  $\geq 2$  days in the first week after injury, with fitted segmented multivariate linear regression model. “2000m1” indicates January of 2000.

Table 3. Interrupted time series models for osmolar agent use for  $\geq 2$  days in the first week after injury

Model Parameters	Hypertonic Saline % (95% Confidence Interval)	Mannitol % (95% Confidence Interval)
Before 9/2000	11.69 (11.20 to 12.17)	21.14 (20.57 to 21.70)
Slope, per month (9/00–6/03)	0.053 (0.031 to 0.075)	0.13 (0.11 to 0.16)
Change with guidelines	2.97 (2.49 to 3.44)	- 4.47 (- 4.99 to - 3.95)
Slope, per month (1/04–12/08)	0.16 (0.13 to 0.19)	- 0.24 (- 0.27 to - 0.22)

TBI care, since only two of 6,238 patients had a billing code for a pediatric rehabilitation floor on the day of admission. Both also had billing codes for mechanical ventilation and ICU stays.

The lag period from July–December, 2003 excluded 444 patients from the interrupted time series models. Hospital mortality for those patients was 19.1%, not different from those not admitted during the lag period ( $p = .664$ ).

Exploratory time series models for hypertonic saline or mannitol use on  $\geq 3$  days in the first week had similar results to the  $\geq 2$  day models (not shown).

We also analyzed hypertonic saline and mannitol use for  $\geq 3$  days (restricted to the  $n = 5607$  patients with length of stay  $\geq 3$  days) in patients with and without ICP monitoring. Of the 1,283 children who received  $\geq 3$  days of hypertonic saline (528 patients), mannitol (478), or both (279), 303 (24%) did not have an ICP monitor (not shown). Of the 233 infants who received  $\geq 3$  days of osmolar therapy, 49% did not have an ICP monitor.

In GEE models restricted to those with ICP monitors, older age, AIS category 4, any skull fracture, and admission after the guidelines were independently associated with hypertonic saline use for  $\geq 2$  days. Older age, any skull fracture, and SDH were independently associated with mannitol use when restricted to those with ICP monitors.

## DISCUSSION

In this large, multicenter database, we found that hypertonic saline and mannitol for pediatric TBI are used more often in older children, those with skull fractures and non-epidural ICH, and those with more severe head injuries; however, substantial variation between hospitals was present. In addition, the 2003 guidelines for the care of children with severe TBI appear to have impacted practice, with increased hypertonic saline use and decreased mannitol use after their publication.

To our knowledge, associations of osmolar therapy use with head injury sever-

ity and age have not been previously reported. It seems logical that osmolar agents are used more often in patients with more severe head injuries, since these patients are more likely to have intracranial hypertension. Osmolar therapy was also much more common in children with ICP monitors, likely the more severely injured patients. Interestingly, approximately one-quarter of the sustained ( $\geq 2$ –3 days in the first week) osmolar therapy we found was in children without ICP monitoring. In infants, approximately half of the sustained osmolar therapy was without ICP monitoring. Morris et al (24) also found that first-tier ICP-targeted therapy (cerebrospinal fluid drainage, osmolar therapy, or mild hyperventilation) was common (35%) in children with severe TBI and no ICP monitor.

The association of osmolar therapy use with age after adjustment for the effect of the published guidelines, between-hospital variation, and injury severity suggests that providers are treating infants as if they are at lower risk for intracranial hypertension, despite a clear statement in the 2003 guidelines that “[t]he presence of open fontanels and/or sutures in an infant with severe TBI does not preclude the development of intracranial hypertension ...” (25) This effect persisted when the analysis was restricted to patients with ICP monitors.

It is impossible to determine which factors caused the changes in hypertonic saline and mannitol use at approximately the time of guideline publication, but interrupted time series analysis is among the most rigorous available quasi-experimental methods to study interventions at a particular time in the past (23, 26–29). Although chosen *a priori*, cluster adjustment for variation across hospitals was necessary given the substantial hospital-level variation we found. Our interrupted time series models, as is typical, did not include patient-level covariates because of the low likelihood that, for example, injury type, changed in July, 2003 at the time of guideline publication (23).

The peak of osmolar therapy use on the second day of admission fit with our understanding of the mechanisms and timing of cerebral edema and intracranial hypertension in children with TBI. However, we were surprised at the relatively constant rate of hypertonic saline use across the first week of hospital care. Prolonged tapers of hypertonic saline to avoid hyponatremia or malignant intracranial hypertension may explain this

Table 4. Multivariate logistic models for osmolar agent use  $\geq 2$  days in the first week after injury

Model Parameters	Hypertonic Saline Adjusted Odds Ratio <sup>a</sup> (95% Confidence Interval)	Mannitol Adjusted Odds Ratio (95% Confidence Interval)
Age		
0 to 364 days	1.00 (ref.)	1.00 (ref.)
1 to <5 yrs	0.93 (0.74–1.16)	1.26 (1.03–1.54)
5 to <13 yrs	1.00 (0.80–1.25)	1.53 (1.28–1.83)
13 to <18 yrs	1.40 (1.06–1.87)	1.81 (1.42–2.30)
Insurance status		
Other	1.00 (ref.)	1.00 (ref.)
Government	1.04 (0.90–1.19)	1.04 (0.86–1.26)
Admission date		
2000–7/2003	1.00 (ref.)	1.00 (ref.)
8/2003–2008	2.08 (1.43–3.01)	0.69 (0.52–0.91)
Any intracranial hemorrhage		
No	1.00 (ref.)	1.00 (ref.)
Yes	1.50 (1.13–1.99)	1.62 (1.30–2.01)
Any skull fracture		
No	1.00 (ref.)	1.00 (ref.)
Yes	1.36 (1.10–1.67)	1.48 (1.18–1.86)
Epidural hematoma, <sup>b</sup> no fracture		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.54 (0.36–0.80)	0.49 (0.28–0.84)
Subdural hemorrhage, <sup>c</sup> no fracture		
No		1.00 (ref.)
Yes		1.34 (1.03–1.75)
Head/neck abbreviated injury scale <sup>d</sup>		
3	1.00 (ref.)	1.00 (ref.)
4	1.26 (0.92–1.73)	1.06 (0.76–1.48)
5 or 6	1.64 (1.17–2.30)	1.95 (1.47–2.60)
Injury severity score <sup>e</sup>		
<15	1.00 (ref.)	1.00 (ref.)
$\geq 15$	1.12 (0.84–1.48)	1.01 (0.80–1.28)

ref., reference category.

<sup>a</sup>Odds Ratio, adjusted for clustering by hospital using generalized estimating equations; <sup>b</sup>epidural hematoma without skull fracture (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes 852.4 and 852.5); <sup>c</sup>subdural hemorrhage without skull fracture (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes 852.2 and 852.3). This variable was not significant in the bivariate analysis for hypertonic saline; <sup>d</sup>abbreviated Injury Scale score, head/neck body region, derived using ICDMAP-90; <sup>e</sup>injury Severity score, derived using ICDMAP-90.

finding. It is possible that the mannitol use for only 1 day in patients with EDH reflects rapid medical stabilization before operative intervention or adoption in the pediatric community of adult recommendations for high-dose emergency department mannitol use based on now-retracted papers by Cruz et al (30–32).

Hypertonic saline may be given to treat hyponatremia from cerebral salt wasting. We analyzed the diagnosis of hyponatremia (there is no ICD-9-CM diagnosis code for cerebral salt wasting) over the same time period, because increased awareness of cerebral salt wasting might increase the use of hypertonic saline. Hyponatremia was diagnosed at a relatively constant rate, and had a slightly decreasing trend after TBI guideline publication, making it unlikely that the increase in hypertonic saline use was due to treatment of hyponatremia. This may also

mean that increasing hypertonic saline use has not resulted in an increase in rebound hyponatremia.

Postresuscitation Glasgow Coma Scale score, pupillary exam, and computed tomography results, the most predictive measures of TBI severity, are not present in the PHIS database. We restricted our analysis using head/neck AIS scores and mechanical ventilation, and ICU billing codes as proxies for severity, but they may not completely represent Glasgow Coma Scale-based severity of TBI. ICDMAP-90, the software package we used to calculate AIS and ISS scores from ICD-9-CM diagnosis codes, has been validated overall (33) and in children (34) for its ability to determine injury severity, and has been successfully used in several studies of children with TBI, including one using the PHIS database (35–37). Coates et al (38) and Di Gennaro et al (39)

also defined their study populations using head AIS scores ( $\geq 3$ ) in analyses of children with TBI.

Despite the absence of Glasgow Coma Scale scores, pupillary exam, and computed tomography results in our dataset, our patients were similar to those in other studies. The in-hospital mortality of our study population (18.8%) compared well with published single-center estimates (22%–24%) and with a multi-center trial without an apparent treatment effect (16.4%, with 8.9% of patients lost to follow-up) (40–43). Some older studies reported higher mortality (44), and a recently published study reported lower mortality (45). The rates of skull fracture (55% vs. 52%) and intracranial hematoma (71% vs. 69%) in our sample compared well with those reported by Hutchison et al (43). The median ISS in our sample was lower (16 vs. 25) than in the work of Coates et al (38) and Zebrack et al (40). Hutchison et al (43) reported higher rates of hypertonic saline and mannitol use (50%–60% for both osmolar agents), but the “usual care” arm of clinical trials may be different from usual care in other settings (43, 46).

There are several other potential limitations to this study, primarily related to our use of an existing database. The PHIS database has advantages over a strictly administrative database, but pharmacy and clinical billing data are only available by day of service, and not, for example, by hour. In addition, the available ICD-9-CM diagnosis codes for TBI do not allow ideal categorization of injury type, and those diagnosis codes were used to derive both injury scores (AIS, ISS) and specific injury types (SDH, EDH, etc).

In conclusion, hypertonic saline and mannitol use in pediatric TBI is higher in older children, those with skull fractures and ICH, and those with more severe head injuries, with substantial variation between hospitals. The patient-level and hospital-level variation, and the significant amount of sustained osmolar therapy without an ICP monitor, particularly in infants, suggest opportunities to improve the quality of pediatric TBI care. The apparent effect of published guidelines on clinical practice in this area suggests that, with limited available high-quality evidence on how to use hypertonic saline and mannitol in children with TBI, providers attempt to follow expert guidelines.

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