Pediatric hypertonic saline use in emergency departments

Hypertonic saline (HTS) is often used to manage cerebral edema and increased intracranial pressure (ICP) in children via creation of an osmolar gradient which promotes decreases in brain interstitial volume along the blood-brain barrier [1]. It also acts as a plasma volume expander. There is scant evidence directing administration in children [2,3,4] resulting in variation in emergency physician practices [5,6]. HTS exhibits low rates of adverse effects, even with the use of intravenous (IV) concentrations through 23.4% [7-9], IV bolus doses up to 24 ml per kilogram (ml/kg) [10], or with administration over 3 min [11-13]. However, hypernatremia is a common side effect of continuous HTS infusion [14,15] and serious adverse events have been reported when infusions are sustained over several days [16-19].

The objectives of this cross-sectional survey were to describe the emergency physician practice variability in HTS administration in children, and to identify enablers and barriers to use with a goal of informing of common practice until quality evidence-based recommendations are derived. The American Academy of Pediatrics Section on Emergency Medicine (AAP-SOEM) and the American College of Emergency Physicians Section of Pediatric Emergency Medicine (ACEP-Peds) approved the electronic survey distribution to their listservs following evaluation for significance and methodology. Surveys were distributed over a consecutive three-month period with up to three reminders after distribution. Consent was implied by survey completion. Participants were instructed to complete the survey only once, regardless of dual memberships with AAP and ACEP. Participants were not compensated. No identifiers were collected. The primary investigator's University Human Rights Protection Office approved this study with a waiver of documented consent.

Survey items were developed to inform domains regarding HTS use: physician knowledge; clinical practice; and perceived barriers to use. Items were generated through literature reviews and interviews with multidisciplinary experts. Items were grouped into domains with subtopic development in use, administration, and dosing. A survey expert led item reduction and question formatting. Survey validity was established using a modified Delphi method. Multidisciplinary experts convened to review and revise survey items. Reliability of the survey was established using test-retest methodology. The survey was pilot-tested among a representative group of emergency medicine physicians caring for children with re-testing for reliability 2 weeks later ($\alpha = 1.0$) and interview to assess their views on the survey's comprehensiveness, clarity, and face validity. The final survey consisted of 22 individual items, and employed anonymous bivariate, multiple choice, and free text responses.

Grouped data and comparisons were made using the Chi-squared test or Fisher Exact test, as appropriate and related to: 1. Level of training (junior physicians were in practice <10 years since training or currently in training); 2. Hospital types were categorized factorially relative to their distinction as a children's hospital and Level 1 Trauma Center; 3. Knowledge base[1]; and 4. Preference for HTS over mannitol.[2] Analyses were run using Stata[3] 14/SE for Windows.

[1] Respondents were identified as knowledgeable of indications for HTS use if they answered anything other than "I prefer not to use osmotic agents" in question A1 (*Appendix A*).

[2] To differentiate between a participant's preference of HTS over mannitol, question A1 (*Appendix A*) was dichotomized such that those who chose answer A were considered preferring HTS, while those who preferred mannitol chose B or C.

[3] StataCorp, LP College Station, TX.

Table 1
Respondent characteristics.

Characteristics	N (%)
N	338
Categorized trauma and children's hospital type	
Level 1 trauma children's hospital	210 (67.1%)
Level 1 trauma non-children's hospital	30 (9.6%)
Non-level 1 trauma children's hospital	51 (16.3%)
Non-level 1 trauma non-children's hospital	22 (7.0%)
Report of academic hospital	282 (90.1%)
Physician type	
Academic Faculty	272 (86.9%)
Completed pediatric residency	227 (67.2%)
Completed emergency medicine residency	47 (13.9%)
Completed pediatric emergency medicine fellowship	263 (77.8%)
Year since completion of last training	
0–5 years	81 (26.1%)
5–10 years	73 (23.5%)
10–15 years	47 (15.1%)
15–20 years	29 (9.3%)
>20 years	74 (23.8%)
Still in training	7 (2.3%)
Level of experience	
Junior physician	161 (51.8%)
Senior physician	150 (48.2%)

Of the 338 respondents, the majority practiced in a Level 1 Trauma Center at a children's hospital and half were junior physicians (Table 1). For the following statistical results see Tables 2–4.

Table 2
Survey responses.

Characteristics	N (%)
N	338
Osmotic agent preferences in pediatric TBI	
IV HTS	177 (52.8%)
HTS only if patient previously hypotensive	9 (2.7%)
IV mannitol	146 (43.6%)
Prefer not to use osmotic agents	3 (0.9%)
Preferred HTS Concentration	
3%	327 (96.8%)
5%	5 (1.5%)
7%	2 (0.6%)
24%	4 (1.2%)
Preferred HTS dose (for those who use 3% HTS)	
1–2 ml/kg	62 (19.0%)
3–4 ml/kg	136 (41.6%)
5–6 ml/kg	105 (32.1%)
7–8 ml/kg	12 (3.7%)
9–10 ml/kg	11 (3.4%)
>10 ml/kg	1 (0.3%)
Preferred method of HTS administration (for those who use 3% HTS)	
Bolus administration via IV only	220 (68.1%)
Continuous IV administration only	23 (7.1%)
Bolus dose following continuous IV administration	80 (24.8%)
Speed of administration if bolus given	
IV push as fast as possible	46 (21.3%)
Over 5–10 min	124 (57.4%)
Over 15–30 min	44 (20.4%)
Over 1 h	2 (0.9%)
Frequency of HTS use in the past year	
1–2 times	144 (47.4%)
3–4 times	32 (10.5%)
5–6 times	19 (6.3%)
>6 times	16 (5.3%)
I have not used it in the past year	93 (30.6%)
Methods of 3% HTS storage	
Pre-packaged concentrations that are sent from pharmacy to ED	93 (32.2%)
Compounded in the pharmacy and sent to ED	27 (9.3%)
Physically stored in ED and accessible for immediate use	169 (58.5%)

Table 3
Differences in HTS practice between junior and senior physicians.

Characteristics	Junior physician (%)	Senior physician (%)	*p*-Value
N (%)	161 (51.8%)	150 (48.2%)	
Prefer HTS over mannitol for pediatric TBI	103 (64.4%)	63 (43.2%)	<0.001
Preferred HTS dose volume (if using 3% HTS)			
1–2 ml/kg	24 (15.4%)	28 (19.2%)	
3–4 ml/kg	71 (45.5%)	55 (37.7%)	
5–6 ml/kg	51 (32.7%)	50 (34.3%)	
≥7 ml/kg	10 (6.4%)	13 (8.9%)	0.491
Method of HTS administration (if using 3% HTS)			
Bolus infusion only	107 (69.0%)	100 (69.0%)	
Continuous IV utilized	48 (31.0%)	45 (31.0%)	0.990
Frequency of HTS use in the past year			
<3 times	113 (74.3%)	116 (82.3%)	
≥3 times	39 (25.7%)	25 (17.7%)	0.101

Most (99.1%) respondents were knowledgeable of osmotic agent indications in increased ICP secondary to traumatic brain injury (TBI). When comparing preferences of mannitol versus HTS in the scenario of pediatric TBI, junior faculty (64.4%) preferred HTS significantly more than senior faculty (43.2%) ($p < 0.001$). HTS was more frequently preferred over mannitol in Level 1 Trauma Centers.

The vast majority of the respondents (96.7%) preferred using HTS at a concentration of 3% and 3-4 mL/kg was the most commonly selected 3% dose-volume option. The most preferred administration route was via IV bolus (68.1%). Among participants who chose to administer 3% HTS as a bolus, 78.7% reported bolus administration over <15 min.

Of all respondents, 99.4% did not observe any clearly attributable side effects from administering HTS. Two respondents (0.6%) reported adverse events; hypotension and central pontine myelinolysis in the setting of chronic hyponatremia correction.

Most respondents (58.5%) reported that HTS was physically stored in the ED and accessible by nursing or pharmacy for immediate use. The majority of Level 1 Trauma children's hospitals (67.9%) stored 3% HTS in a readily available formulation within the ED.

Current literature supports that HTS is the first-line drug for treating increased ICP, associated with more favorable cerebral hemodynamics and fastest resolution of increased ICP [20,21]. A 2015 meta-analysis concluded that HTS is more effective than mannitol in decreasing ICP secondary to TBI in adults, without a difference in serum osmolarity [22]. However, a 2016 meta-analysis determined there was no difference in *mean* ICP reduction in adults, though HTS had fewer failures in ICP reduction than mannitol [23]. Both osmotic agents temporarily augment cardiac output, though mannitol is associated with subsequent diuresis [24]. Animal models conclude that HTS results in similar fluid resuscitative end-points as double the volume of normal saline [25]. Current guidelines for the management of severe TBI in children admitted to in-patient critical care settings recommend HTS doses of 6.5-10 ml/kg, however the data supporting this dosage comes from a single small trial of 18 children in an intensive care unit setting from 1990 [26,27].

This survey described wide variations in storage preferences by hospital type possibly related to Joint Commission advisements [28], space, and hospital regulations. The Joint Commission advises that "it may be necessary to store concentrated electrolytes in specific patient care areas….[and] decisions should be based on the results of a robust risk assessment followed by implementation of appropriate safeguards…" Safeguards suggested are segregation from medications, limits to the amount stored; use of warning labels; and restricted access [29]. Given that systolic blood pressures less than the 75th percentile in children with acute severe TBI are associated with a higher risk of in-hospital mortality, we propose the storage of 3% HTS in EDs for ease of rapid administration over <15 min in the treatment of increased ICP due to its added benefit of plasma volume expansion [30].

Prior presentations

None.

Funding sources/disclosures

None/no disclosures.

Acknowledgments

None.

Table 4
Difference in HTS practice between varying hospital types.

Characteristics	Level 1 trauma children's hospital (%)	Level 1 trauma non-children's hospital (%)	Non-Level 1 trauma children hospital (%)	Neither Level 1 trauma nor children's hospital (%)	p-Value
N (%)	210 (67.1%)	30 (9.6%)	51 (16.3%)	22 (7.0%)	
Prefer HTS over mannitol for pediatric TBI	126 (60.3%)	19 (63.3%)	27 (56.3%)	10 (47.6%)	0.025
Preferred HTS dose volume (if using 3% HTS)					
1–2 ml/kg	27 (13.0%)	9 (32.1%)	11 (22.9%)	5 (25.0%)	
3–4 ml/kg	82 (39.4%)	14 (50.0%)	20 (41.7%)	10 (50.0%)	
5–6 ml/kg	81 (38.9%)	4 (14.3%)	15 (31.3%)	2 (10.0%)	
≥7 ml/kg	18 (8.7%)	1 (3.6%)	2 (4.2%)	3 (15.0%)	0.011
Method of HTS administration (if using 3% HTS)					
Bolus infusion only	152 (73.4%)	18 (64.3%)	25 (52.1%)	14 (73.7%)	
Continuous IV utilized	55 (26.6%)	10 (35.7%)	23 (47.9%)	5 (26.3%)	0.032
Frequency of HTS use in the past year					
<3 times	150 (74.6%)	23 (88.5%)	38 (80.9%)	20 (95.2%)	
≥3 times	51 (25.4%)	3 (11.5%)	9 (19.2%)	1 (4.8%)	0.076
Current 3% HTS storage preferences					
Stored in the pharmacy as pre-packaged concentrations	52 (26.9%)	11 (40.7%)	20 (41.7%)	10 (47.6%)	
Compounded in the pharmacy and send to ED	10 (5.2%)	4 (14.8%)	8 (16.7%)	5 (23.8%)	
Stored and Accessible in the ED	131 (67.9%)	12 (44.4%)	20 (41.7%)	6 (28.6%)	<0.001

Author contributions

AL and RM conceived the study and designed the trial. AL supervised the conduct of the trial and data collection. AL undertook recruitment of organizations and managed the data, including quality control. KN and RM provided statistical advice on study design and analyzed the data; KN chaired the data oversight committee. KN and AL drafted the manuscript, and all authors contributed substantially to its revision. KN and AL takes responsibility for the paper as a whole.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.09.040.

Kian Niknam
Stanford University School of Medicine, Department of Emergency Medicine, United States of America

Rakesh Mistry, MD
University of Colorado, Department of Pediatrics, United States of America

Angela Lumba-Brown, MD
Stanford University School of Medicine, Department of Emergency Medicine, United States of America
Corresponding author at: 900 Welch Road - #350/MC: 5119, Palo Alto, CA 94304, United States of America.
E-mail addresses: alumba@stanford.edu.

10 September 2018

https://doi.org/10.1016/j.ajem.2018.09.040

References

[1] Hinson HE, Stein D, Sheth KN. Hypertonic saline and mannitol therapy in critical care neurology. J Intensive Care Med Jan-Feb 2013;28(1):3–11.
[2] Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol 1992;4(1):4–10.
[3] Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 2012;13(Suppl. 1):S1–82. https://doi.org/10.1097/PCC.0b013e31823f435c.
[4] Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol 1992;4(1):4–10.
[5] Berger Pelletier E, Emond M, Lauzier F, Savard M, Turgeon AF. Hyperosmolar therapy in severe traumatic brain injury: a survey of emergency physicians from a large Canadian province. PLoS One 2014;9(4):e95778.
[6] Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 2012;13(Suppl. 1):S1–82. https://doi.org/10.1097/PCC.0b013e31823f435c.
[7] Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 2012;13(Suppl. 1):S1–82. https://doi.org/10.1097/PCC.0b013e31823f435c (Epub 2012/01/11, PubMed PMID: 22217782).
[8] Kerwin AJ, Schinco MA, Tepas 3rd JJ, Renfro WH, Vitarbo EA, Muehlberger M. The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. J Trauma 2009;67(2):277–82. https://doi.org/10.1097/TA.0b013e3181acc726 [Epub 2009/08/12, PubMed PMID: 19667879].
[9] Nakagawa K, Chang CW, Koenig MA, Yu M, Tokumaru S. Treatment of refractory intracranial hypertension with 23.4% saline in children with severe traumatic brain injury. J Clin Anesth 2012;24(4):318–23 Epub 2012/05/23 https://doi.org/10.1016/j.jclinane.2011.10.011. [PubMed PMID: 22608588].
[10] Luu JL, Wendtland CL, Gross MF, Mirza F, Zouros A, Zimmerman GJ, et al. Three-percent saline administration during pediatric critical care transport. Pediatr Emerg Care 2011;27(12):1113–7. https://doi.org/10.1097/PEC.0b013e31823aff59 [PubMed PMID: 22134236, Epub 2011/12/03].
[11] Brenkert TE, Estrada CM, McMorrow SP, Abramo TJ. Intravenous hypertonic saline use in the pediatric emergency department. Pediatr Emerg Care 2013;29(1):71–3. https://doi.org/10.1097/PEC.0b013e31827b54c3 [Epub 2013/01/04, PubMed PMID: 23283268].
[12] Luu JL, Wendtland CL, Gross MF, Mirza F, Zouros A, Zimmerman GJ, et al. Three-percent saline administration during pediatric critical care transport. Pediatr Emerg Care 2011;27(12):1113–7. https://doi.org/10.1097/PEC.0b013e31823aff59 [Epub 2011/12/03, PubMed PMID: 22134236].
[13] Lumba-Brown A, Harley J, Lucio S, Vaida F, Hilfiker M. Hypertonic saline as a therapy for pediatric concussive pain: a randomized controlled trial in the emergency department. Pediatr Emerg Care 2014;30(3):139–45.
[14] Khanna S, Davis D, Peterson B, Fisher B, Tung H, O'Quigley J, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit Care Med 2000;28(4):1144–51 [Epub 2000/05/16. PubMed PMID: 10809296].
[15] Peterson B, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. Crit Care Med 2000;28(4):1136–43 [Epub 2000/05/16. PubMed PMID: 10809295].
[16] Gonda DD, Meltzer HS, Crawford JR, Hilfiker ML, Shellington DK, Peterson BM, et al. Complications associated with prolonged hypertonic saline therapy in children with elevated intracranial pressure. Pediatr Crit Care Med 2013;14(6):610–20. https://doi.org/10.1097/PCC.0b013e318291772b [Epub 2013/07/05, PubMed PMID: 23823197].
[17] Froelich M, Ni Q, Wess C, Ougorets I, Hartl R. Continuous hypertonic saline therapy and the occurrence of complications in neurocritically ill patients. Crit Care Med 2009;37(4):1433–41. https://doi.org/10.1097/CCM.0b013e31819c1933 [Epub 2009/02/27, PubMed PMID: 19242317].
[18] Hartl R, Medary MB, Ruge M, Arfors KE, Ghahremani F, Ghajar J. Hypertonic/hyperoncotic saline attenuates microcirculatory disturbances after traumatic brain injury. J Trauma 1997;42(5 Suppl):S41–7 [Epub 1997/05/01. PubMed PMID: 9191695].
[19] Coimbra R, Hoyt DB, Junger WG, Angle N, Wolf P, Loomis W, et al. Hypertonic saline resuscitation decreases susceptibility to sepsis after hemorrhagic shock. J Trauma 1997;42(4):602–6 discussion 6-7. [Epub 1997/04/01, PubMed PMID: 9137245].
[20] Shein SL, Ferguson NM, Kochanek PM, Bayir H, Clark RS, Fink EL, et al. 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. Pediatr Crit Care Med 2016;17(3):236–45. https://doi.org/10.1097/pcc.0000000000000610.
[21] Rickard AC, Smith JE, Newell P, Bailey A, Kehoe A, Mann C. Salt or sugar for your injured brain? A meta-analysis of randomised controlled trials of mannitol versus hypertonic sodium solutions to manage raised intracranial pressure in traumatic brain injury. Emerg Med J 2014;31(8):679–83. https://doi.org/10.1136/emermed-2013-202679.
[22] Li M, Chen T, Chen SD, Cai J, Hu YH. Comparison of equimolar doses of mannitol and hypertonic saline for the treatment of elevated intracranial pressure after traumatic brain injury: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94(17):e736. https://doi.org/10.1097/md.0000000000000736.
[23] Burgess S, Abu-Laban RB, Slavik RS, Vu EN, Zed PJ. A systematic review of randomized controlled trials comparing hypertonic sodium solutions and mannitol for traumatic brain injury: implications for emergency department management. Ann Pharmacother 2016;50(4):291–300. https://doi.org/10.1177/1060028016628893.
[24] Tsaousi G, Stazi E, Cinicola M, Bilotta F. Cardiac output changes after osmotic therapy in neurosurgical and neurocritical care patients: a systematic review of the clinical literature. Br J Clin Pharmacol 2018;84(4):636–48. https://doi.org/10.1111/bcp.13492.
[25] Urbano J, Lopez-Herce J, Solana MJ, Del Castillo J, Botran M, Bellon JM. Comparison of normal saline, hypertonic saline and hypertonic saline colloid resuscitation fluids in an infant animal model of hypovolemic shock. Resuscitation 2012;83(9):1159–65. https://doi.org/10.1016/j.resuscitation.2012.02.003.
[26] Kochanek PM, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents—second edition. Pediatr Crit Care Med 2012;13(Suppl. 1):S1–82. https://doi.org/10.1097/PCC.0b013e31823f435c.
[27] Fisher B, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. J Neurosurg Anesthesiol 1992;4(1):4–10.
[28] The joint commission website. https://www.jointcommission.org/about_us/about_the_joint_commission_main.aspx, Accessed date: 30 August 2018.
[29] The joint commission website. https://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFAQId=1534, Accessed date: 30 August 2018.
[30] Suttipongkaset P, Chaikittisilpa N, Vavilala MS, Lele AV, Watanitanon A, Chandee T, et al. Blood pressure thresholds and mortality in pediatric traumatic brain injury. Pediatrics 2018;142(2). https://doi.org/10.1542/peds.2018-0594.

Should we believe emergency department patients self-reported tetanus vaccine status?

Immunization surveying is the milestone in prevention of diseases and screening for populations at risk yet its reliability needs to be