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Authors

Pohl, Charles E

Harvey, Helen

Foley, Jennifer

et al.

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Peripheral IV Administration of Hypertonic Saline: Single-Center Retrospective PICU Study

Charles E. Pohl, MD[1,2], **Helen Harvey, MD**[1], **Jennifer Foley, RN**[1], **Euyhyun Lee, MS**[3], **Ronghui Xu, PhD**[4], **Nicole F. O'Brien, MD**[4], **Nicole G. Coufal, MD, PhD**[1,2]

[1]Division of Pediatric Critical Care, Rady Children's Hospital, San Diego, CA.

[2]Department of Pediatrics, University of California at San Diego, La Jolla, CA.

[3]Altman Clinical and Translational Research Institute, University of California at San Diego, La Jolla, CA.

[4]Division of Critical Care Medicine, Nationwide Children's Hospital, The Ohio State University, Columbus, OH.

Abstract

OBJECTIVES: To determine the frequency and characteristics of complications of peripherally administered hypertonic saline (HTS) through assessment of infiltration and extravasation.

DESIGN: Retrospective cross-sectional study.

SETTING: Freestanding tertiary care pediatric hospital.

PATIENTS: Children who received HTS through a peripheral IV catheter (PIVC).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We conducted a single-center retrospective review from January 2012 to 2019. A total of 526 patients with 1,020 unique administrations of HTS through a PIVC met inclusion criteria. The primary endpoint was PIVC failure due to infiltration or extravasation. The indication for the administration of HTS infusion was collected. Catheter data was captured, including the setting of catheter placement, anatomical location on the patient, gauge size, length of time from catheter insertion to HTS infusion, in situ duration of catheter lifespan, and removal rationale. The administration data for HTS was reviewed and included volume of administration, bolus versus continuous infusion, infusion rate, infusion duration, and vesicant medications administered through the PIVC. There were 843 bolus infusions of HTS and 172 continuous infusions. Of the bolus administrations, there were eight infiltrations (0.9%). The continuous infusion group had 13 infiltrations (7.6%). There were no extravasations in either group, and no patients required medical therapy or intervention by the wound care or plastic surgery teams. There was no significant morbidity attributed to HTS administration in either group.

For information regarding this article, Cepohl89@gmail.com.

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CONCLUSIONS: HTS administered through a PIVC infrequently infiltrates in critically ill pediatric patients. The infiltration rate was low when HTS is administered as a bolus but higher when given as a continuous infusion. However, no patient suffered an extravasation injury or long-term morbidity from any infiltration.

Keywords

extravasation; hypertonic saline; infiltration; medication complications; pediatric; peripheral intravenous catheter

Administration of three percent hypertonic saline (HTS) through a peripheral IV catheter (PIVC) has historically been discouraged due to the theoretical risk of infiltration and extravasation caused by administration of a vesicant into a peripheral vein. Risk factors for extravasation injury include extremes of age, anatomical location of infusion sites (risk is higher if periarticular or lower extremity due to increased likelihood of dislodgement), and properties of the drug including cytotoxicity, pH, and osmolality (1, 2). Human serum osmolarity is 290 mOsm/L (285–310 mOsm/L) with a pH between 7.35 and 7.45 (1). Infusions with a pH range outside of 5.5–8.5 and a higher osmolarity than plasma are more likely to cause damage to endothelial tissues and injury to soft tissues in cases of infiltration (1, 2). Studies have found that solutions with osmolarity greater than 1,000 mOsm/L have a significant association with phlebitis and infiltration (3). HTS has an average pH of 5 (range, 4.5–7.0) and an osmolarity of 1,027 (4), placing it marginally outside the reported clinical safety range for peripheral administration.

Despite these safety concerns, there is clinical evidence to support that HTS administration through a PIVC is safe. Several studies in adult patients have demonstrated that peripheral infusion of HTS carried a low risk of minor complications (5–8). Furthermore, these studies noted reduced complications of central line placement including deep venous thrombosis, hematoma, arrhythmia, bloodstream infection, pneumothorax, and venous or arterial vessel injury (9). In 2018, a prospective observational study in adults compared continuous infusion of PIVC HTS of greater than 4 hours duration and routine catheter solutions (nonvesicants) across 291 catheters and determined that the rate of phlebitis and PIVC failure were no different between infusion types (10). There is minimal data evaluating the frequency of complication when HTS is administered through a PIVC in the pediatric population. Two small studies report on peripheral administration of HTS in children during emergency transport and in the emergency department as a one-time bolus (11, 12). Neither study included children outside the emergency department or those receiving multiple HTS boluses or HTS administered as a continuous infusion. Given the paucity of literature on this topic, as well as the increasing data regarding efficacy and utility of HTS in traumatic brain injury, the purpose of this study was to evaluate the frequency of complications associated with administration of HTS through a PIVC both as a bolus dose and as an infusion in critically ill children. We hypothesized that peripherally administered HTS results in minimal complications.

METHODS

This study was approved by the Institutional Review Board at the University of California San Diego (Number 190065X) and Rady Children's Hospital San Diego (Number 4248) on March 20, 2019. This was approved with a nonsignificant risk determination, which led to a waiver of informed consent.

This is a retrospective single-center study at a tertiary children's hospital. The electronic health record (EHR) was queried for patients with "peripheral IV" and the medication "hypertonic saline" or synonyms to "hypertonic saline." The PIVC HTS cohort included those patients that were administered 3% HTS through a PIVC at least once. The central HTS group received HTS exclusively through a central venous line (CVL). Administrations were excluded from analysis if HTS was administered through a central venous catheter, the medication was ordered but not infused, or key aspects of documentation were incomplete (medication administration was not explicitly associated with a PIVC while a central catheter was in place). In patient administrations were obtained from January 1, 2012, to January 1, 2018, and administrations occurring during transport from July 21, 2016, to December 31, 2018. This included patients 1 day to 23 years old on all inpatient units and services, as well as patients administered HTS specifically during critical care transport to the hospital. This encompassed all available EHR data at our institution at the time of query, all available data were included; however, in some instances, nursing documentation was incomplete. Patients who were admitted two or more times within the study duration (with PIVC administration of HTS on each hospitalization) were included in the study for their first encounter, but their data were excluded for subsequent hospital admissions.

The primary endpoints were PIVC failure due to infiltration or extravasation injury as a complication of HTS administration within 1 hour of completion of administration. An infiltration was defined as a substance (in this study HTS) that passes through the catheter and permeates into the extravascular tissues instead of the endovascular space. An extravasation injury was defined as an infiltration of medication into the soft tissues, which causes serious injury with potential for permanent harm. Infiltration and extravasation were determined through clinical documentation by the bedside nurse and recorded as swelling, pain, edema, or permanent tissue injury at the site of administration. Qualitative data describing the site of infiltration or extravasation was collected from documented bedside observations. The endpoint of infiltration was assessed following each individual bolus; for continuous infusions complications were considered during and up to 1 hour after infusion was completed. This grading system included the presence or absence of erythema, site palpation (soft, tense, or indurated), pain, slight, or significant swelling, and adequate or impaired distal perfusion. Interventions undertaken after PIVC failure were noted, including the administration of medical therapy or interventions by the wound care or plastic surgery team.

Patients received HTS as a bolus or continuous infusion. We defined a bolus administration as completing within 60 minutes, and a continuous infusion was defined as an infusion with a duration of 60 minutes or longer. The indication for administration of HTS was also collected. If multiple indications for HTS administration were documented in the

medical record, all relevant factors were included. Catheter data was captured, including information on the setting and anatomic location of placement, the size and gauge, the in vivo dwell time until HTS administration, the in situ duration of catheter lifespan, and the reason for removal. The administration data for HTS was reviewed and included volume of administration, bolus or continuous infusion, rate of infusion (reported as an average of mL/kg/hr due to the varying rates of infusion over time), duration of infusion (hr), and the number of HTS doses administered through the PIVC. Vesicant medications (detailed in Supplementary Table 1, http://links.lww.com/PCC/B980) were screened for in each administration of HTS. In our cohort, subsequent doses of HTS were found to be the only vesicant medication administered through PIVC.

Continuous variables and categorical variables are presented as mean or median (sd) count (percentages), respectively. Subject level demographic categorical variables (gender and transport) and continuous variable (age) were analyzed using Fisher exact test and two sample *t* test, respectively. The effect of HTS administration, catheter size, infusion rate of HTS, and the number of HTS boluses given through a PIVC on the presence of complication during infusion were analyzed using a univariable generalized estimation equation model with a binomial distribution and an exchangeable correlation structure. Administrations of HTS with missing data were omitted from statistical analysis, and the *n* value was provided for each analysis reported with the tables. Statistical analyses were performed using R (Version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient demographic data are reported in Table 1, with PIVC characteristics reported in Table 2 and Supplementary Table 2 (http://links.lww.com/PCC/B981). A total of 1,071 patients received HTS during the study period, of which 526 patients were identified as receiving PIVC HTS (Fig. 1). Of note, some patients administered PIVC HTS also received centrally administered HTS at other/later times. Overall, two patients were excluded because of incomplete documentation such that it was unclear if HTS was administered peripherally or centrally, and four patients were excluded when HTS was ordered but never administered. At our institution, HTS is administered preferentially through a CVL but may be administered through a PIVC in emergent situations or at the discretion of the attending critical care physician when a CVL is not in place. The primary indications for HTS administration were altered mental status (n = 346, 16.8%), intracranial hemorrhage (n = 315, 15.3%), concussion (n = 304, 14.7%), and increased intracranial pressure (n = 259, 12.5%) (Table 3).

Among the 526 unique patients receiving PIVC HTS at least once, there were 843 bolus administrations of HTS and 172 continuous infusions, for a total of 1,020 administrations of HTS. Of the 1,020 administrations, there were a total of 21 infiltrations (2.1%) between the two groups. Of the bolus administrations of HTS, there were eight infiltrations (0.9%). Of the continuous infusions of HTS, there were 13 infiltrations (7.6%) (Supplementary Fig. 1, http://links.lww.com/PCC/B982). The overall frequency of all complications during the study period was 3.802% (95% CI, 2.48–5.80%). There were no extravasations in either group, and no patients required medical therapy (such as hyaluronidase injection) or

intervention by the wound care team or plastic surgery. There was no significant morbidity related to infiltration in this study. When separating HTS bolus and continuous groups in the analysis, it was found that administrations given as a bolus of HTS were 89.1% less likely to have a complication compared with an administration of a continuous infusion ($p < 0.001$). A Kaplan-Meier analysis for the duration of HTS administration was not significant (Mantel-Cox test $\chi^2 = 0.1834$; $p = 0.263$) with a median duration of administration of 11 hours for patients with complication and 13.1 for patients without (Supplementary Fig. 2, http://links.lww.com/PCC/B983).

On univariable analysis of the HTS bolus infusion group, administrations of HTS that resulted in infiltration had a higher mean volume of administration (300.5 vs 220.8 mL), lower mean infusion rate (7.8 vs 10.6 mL/kg/hr), and lower mean number of HTS doses administered (2.3 vs 2.8) compared with the group without infiltration. However, on univariable analysis, these risk factors were not statistically significant (Table 4). When evaluating the basic demographics for the continuous HTS infusion group, administrations with infiltration compared with those without infiltration had a lower mean volume of administration (790.9 vs 854.6 mL) and a higher mean infusion rate (1.6 vs 1.4 mL/kg/hr). On univariable analysis, none of these factors remained statistically significant (Table 4).

Serum sodium levels were recorded prior to and following bolus administrations of HTS. Serum sodium levels were found to increase from a preinfusion mean of 138 mEq/L to a post infusion mean of 143 mEq/L ($p \leq 0.001$) (Table 4).

DISCUSSION

HTS is used in a variety of acute settings. Traditionally, due to concerns about infiltration or extravasation, use has been limited to central venous administration. Due to limited data availability for the use of HTS in PIVCs in children, we performed a large retrospective study of peripheral administration of HTS to assess for the occurrence of complications. Overall, 526 patients received at least one dose of PIVC HTS. In this study of 526 patients with 1,020 individual administrations of HTS, there were 21 (2.1%) infiltrations during or within 1 hour of completion of administration of HTS (0.9% of those receiving a bolus dose and 7.6% of those receiving a continuous infusion). The most common morbidities were short-term pain and swelling of the affected area. There was no loss of distal perfusion or devitalization of tissues documented in the study, and no patient required a medical or surgical intervention following infiltration. Given the low frequency of complications from HTS administration through a PIVC, the study was not powered to identify specific risk factors for patients in our cohort.

The results of this study are in alignment with previously published adult and pediatric literature on complications associated with HTS infusions through PIVC. However, this study represents the largest pediatric patient cohort for peripheral HTS administration. Adult studies first pioneered the literature on HTS administrations (5–8), followed by investigations in pediatric transport and emergency medicine (11, 12). Infusion-related events attributed to administration of HTS through PIVC in adults range from 6% to 7% (5, 6, 8). Brenkert et al (10) demonstrated in the pediatric emergency department

setting that in 56 patients, no adverse events related to PIVC HTS administered as a bolus were observed. Similar evidence was produced by Luu et al (12) in 101 patients in the pediatric transport population, where no complications related to the delivery of bolus dose HTS through a PIVC were reported. Compared with the other pediatric studies, our investigation incorporates a significantly larger sample size of 526 patients with 1,020 unique administrations of HTS, it is the first study to evaluate patients outside the emergency department and the first to evaluate patients receiving bolus and continuous infusions of HTS.

The higher rate of PIVC failure we identified with continuous infusion is consistent with the experimental data published by Kuwahara et al (13) that concluded that the duration of a vesicant medication administration is directly proportional to the rate of PIVC infiltration in animal models. The longer the exposure to the vesicant medication, the greater the risk of endothelial tissue injury, and the increased likelihood of loss of endovascular integrity and medication infiltration (2). While our data were unable to independently identify infusion rate and infusion volume as risk factors for complication, this conclusion is limited by the small number of complications and would be better evaluated with a larger sample size of infiltrations or extravasations. Future prospective studies isolating the two variables are recommended to provide further insight.

Study limitations included the retrospective study design. This resulted in incomplete data for some of our secondary endpoints. Additionally, with the small number of infiltrates, we were unable to achieve statistical significance for identification of possible risk factors. Due to the highly skewed outcome, we were unable to perform multivariable analysis with these dataset. A future study with a larger sample of administrations and complications is necessary to achieve statistical significance.

Given these results, it is reasonable to consider bolus administrations of HTS in pediatric patients a practice with minimal risk of significant harm. Continuous HTS infusions may also be considered under appropriate circumstances, with the recognition of a higher risk of infiltration compared with a bolus infusion.

HTS administered through a PIVC has a low frequency of infiltrations in critically ill pediatric patients regardless of PIVC catheter size or location. The infiltration rate is low when HTS is administered as a bolus but higher when administered as a continuous infusion. However, no patient suffered an extravasation injury or long-term morbidity from any infiltration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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This study was approved by the Institutional Review Board at the University of California San Diego and a nonsignificant risk determination led to a waiver of informed consent (University of California San Diego Project Number 190065X and Rady Children's Hospital San Diego Number 4248).

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AT THE BEDSIDE

- This study represents the largest pediatric patient cohort for peripheral HTS administration.
- In this study of 526 patients with 1,020 administrations of HTS, there were 21 (2.1%) infiltrations within one hour of administration of HTS (0.9% of those receiving a bolus dose and 7.6% of those receiving a continuous infusion).
- HTS administered through a PIVC infrequently infiltrates in critically ill pediatric patients.

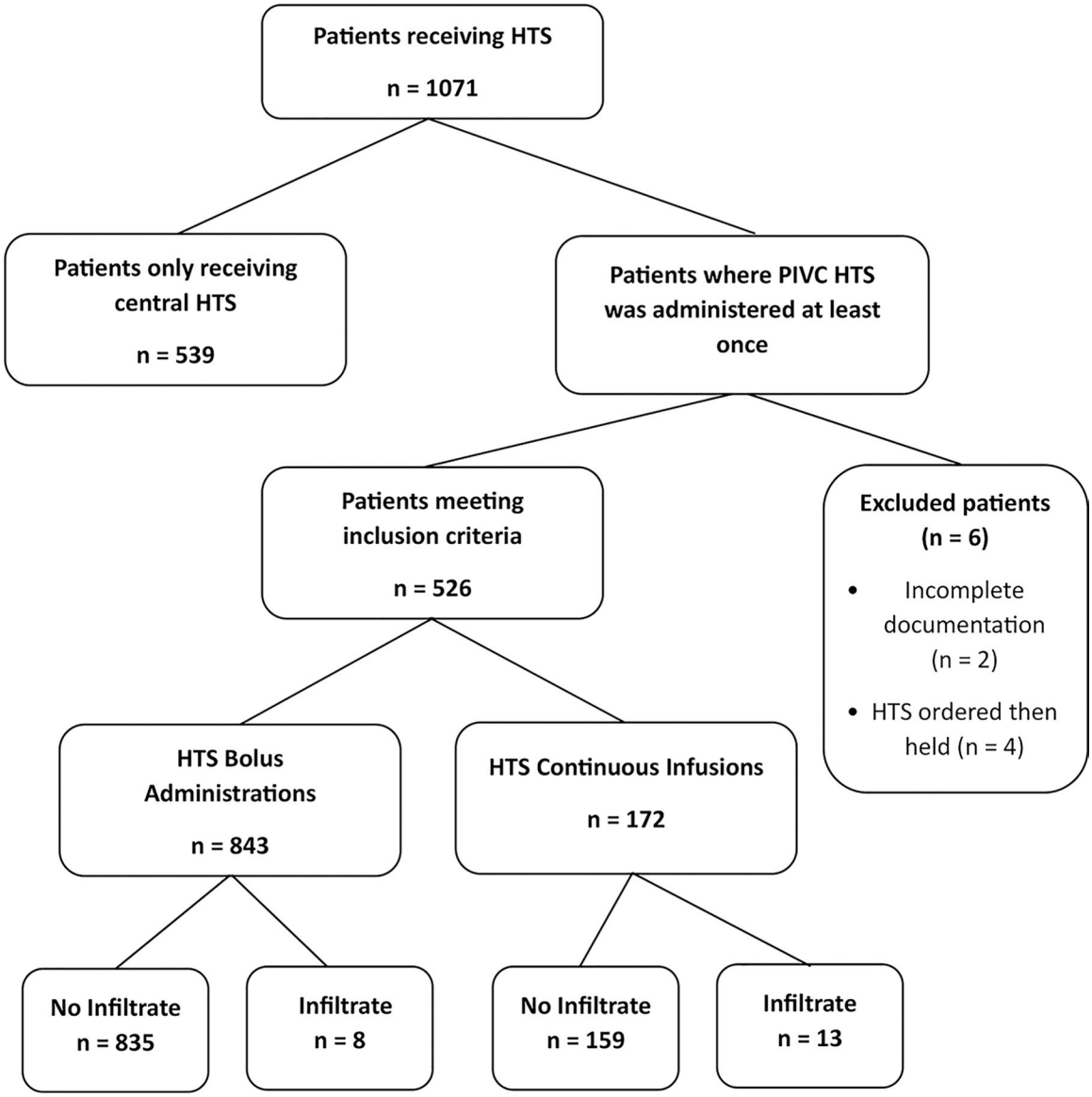

Figure 1.

Inclusion and exclusion of patients receiving hypertonic saline (HTS) through a peripheral IV catheter (PIVC).

TABLE 1.

Demographics of Peripheral IV Catheter Hypertonic Saline by Complication Outcome

Variable	Total	Complication		*p*
		None	Present	
Age[a]	*n* = 526	*n* = 506	*n* = 20	
	8.9 (3.7–13.8)	8.9 (3.7–13.9)	9.5 (3.4–12.8)	0.690
Female[b]	216 (41.1)	210 (97.2)	6 (2.8)	0.360
Male[b]	310 (58.9)	296 (95.5)	14 (4.5)	
Received HTS during transport[b]				
Not transported	487 (92.6)	467 (95.9)	20 (4.1)	0.387
Transported	39 (74)	39 (100)	0 (0)	
Hypertonic saline infusions[b]	*n* = 1,020	*n* = 999	*n* = 21	
Continuous administration	172 (16.9)	159 (15.9)	13 (61.9)	
Bolus administration	843 (82.6)	835 (83.6)	8 (38.1)	
Unknown	5 (0.5)	5 (0.5)	0 (0.0)	
Hypertonic saline volume[c]	*n* = 1,014	*n* = 993	*n* = 21	
	328.1 (525.8)	322.2 (522.4)	604.1 (620.2)	
Continuous administration	*n* = 171	*n* = 158	*n* = 13	0.758
	849.7 (1,026.7)	854.6 (1,049.5)	790.92 (720.5)	
Bolus administration	*n* = 842	*n* = 834	*n* = 8	0.033
	221.6 (230.2)	220.8 (230.4)	300.5 (1974)	
Hypertonic saline infusion rate[d]	*n* = 221	*n* = 206	*n* = 15	
	4 (8.3)	4.2 (8.6)	2.4 (2.4)	
Continuous administration	*n* = 157	*n* = 144	*n* = 13	0.651
	1.4 (1)	1.4 (1)	1.6 (0.6)	

Variable	Total	Complication		*p*
		None	Present	
Bolus administration	*n* = 64	*n* = 62	*n* = 2	0.517
	10.5 (13.4)	10.6 (13.6)	78 (3.2)	
Hypertonic saline infusion duration[e]	*n* = 157	*n* = 144	*n* = 13	0.783
	16.8 (12.9)	16.8 (12.9)	16.5 (12.8)	
Catheter size[f]	*n* = 860	*n* = 841	*n* = 19	
	22 (2.0)	22 (2.0)	22 (2.5)	
Continuous administration[g]	*n* = 150	*n* = 139	*n* = 11	0.368
	21.4 (2)	21.4 (2)	21.1 (2.6)	
Bolus administration[g]	*n* = 707	*n* = 699	*n* = 8	0.997
	21.4 (2)	21.4 (2)	21.5 (2.6)	
Number of coadministrations of HTS through a single peripheral IV catheter (vesicant medication)[g]	*n* = 374	*n* = 369	*n* = 5	
	2.8 (1.2)	2.8 (1.2)	2.2 (0.5)	

HTS = hypertonic saline.

[a] Data are in median yr (Q1–Q3).

[b] Data are *n* (%).

[c] Data are in mean mL (SD).

[d] Data are in mean mL/hr (SD).

[e] Data are in mean hr (SD).

[f] Data are in median gauge size (SD).

[g] Data are in mean (SD).

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TABLE 2.

Peripheral IV Catheter Characteristics

Variable	Frequency	Complication	
		None	Present
Setting of catheter placement[a]	*n* = 1,020	*n* = 999	*n* = 21
Pediatric emergency department	352 (34.5)	344 (97.7)	8 (2.3)
PICU	203 (19.9)	195 (96.1)	8 (3.9)
Referring hospital	133 (13.0)	130 (97.7)	3 (2.3)
Emergency medical services or critical care transport	76 (75)	76 (100)	0 (0)
Operating room department	24 (2.4)	24 (100)	0 (0)
Pediatric wards	6 (0.6)	6 (100)	0 (0)
Neonatal ICU	6 (0.6)	6 (100)	0 (0)
Not documented	220 (21.6)	218 (99.1)	2 (0.9)
Catheter gauge size[a]	*n* = 1,020	*n* = 999	*n* = 21
24G	168 (16.5)	164 (97.6)	4 (2.4)
22G	403 (39.5)	393 (97.5)	10 (2.5)
20G	173 (170)	172 (99.4)	1 (0.6)
18G	98 (9.6)	96 (98)	2 (2)
16G	17 (1.7)	15 (88.2)	2 (11.8)
14G	1 (0.1)	1 (100)	0 (0)
Not documented	160 (15.7)	158 (98.8)	2 (1.3)
Anatomical location of catheter[a]	*n* = 1,020	*n* = 999	*n* = 21
Antecubital	455 (44.6)	452 (45.3)	3 (14.3)
External jugular	3 (0.3)	3 (0.3)	0 (0.0)
Foot	38 (3.7)	37 (3.7)	1 (4.8)
Forearm	70 (6.9)	67 (6.7)	3 (14.3)
Hand	354 (34.7)	341 (34.1)	13 (61.9)
Scalp	2 (0.2)	1 (0.1)	1 (4.8)
Unknown	98 (9.6)	98 (9.8)	0 (0.0)

[a] Data are *n* (%).

TABLE 3.

Indication for Peripheral IV Catheter Hypertonic Saline

Variable	Frequency
Indication for hypertonic saline administration	*n* = 2,065
Altered mental status	346
Intracranial hemorrhage	315
Concussion	304
Increased intracranial pressure	259
Hyponatremia	137
Low Glasgow Coma Scale	137
Seizure	88
Intracranial mass	88
Other	83
Cerebral edema: Diabetic ketoacidosis	65
Hydrocephalous	57
Meningitis	58
Traumatic brain injury	56
Cerebral edema: other	47
Pupillary changes	15
Intracranial abscess	10

Note that patients may have more than one indication for hypertonic saline administration.

TABLE 4.

Univariable Generalized Estimating Equation Outcome for Predicting Complication Outcomes of Peripheral IV Catheter Hypertonic Saline

Bolus Administration of Hypertonic Saline	**Estimate**	**Robust SE**	**Robust *z* Score**	***P***	**OR (95% CI)**
Catheter gauge size					
Catheter size	−0.003	0.236	−0.014	0.989	0.997 (0.627–1.584)
Hypertonic saline volume (mL)					
Hypertonic saline volume	0.001	0	2.128	0.033	1.001 (1.000–1.001)
Hypertonic saline infusion rate (mL/kg/hr)					
Hypertonic saline infusion rate	−0.06	0.093	−0.648	0.517	0.941 (0.784–1.130)
Number of coadministrations of HTS through a single peripheral IV catheter (vesicant medication)	−0.402	0.287	−1.398	0.162	0.669 (0.381–1.175)
Continuous Administration of Hypertonic Saline	**Estimate**	**Robust SE**	**Robust *z* Score**	***P***	**OR (95% CI)**
Catheter gauge size					
Catheter size	0.126	0.14	0.901	0.368	1.135 (0.862–1.494)
Hypertonic saline volume					
Hypertonic saline volume	0	0	−0.308	0.758	1 (1.000–1.000)
Hypertonic saline infusion rate					
Hypertonic saline infusion rate	0.085	0.187	0.452	0.651	1.088 (0.754–1.570)
Hypertonic saline duration (hr)					
Hypertonic saline duration	0.006	0.02	0.275	0.783	1.006 (0.967–1.046)
Generalized Estimation Equation Outcome Predicting Change in Score Following HTS	**Estimate**	**Robust se**	**Robust z Score**	**p**	
Serum sodium level					
Serum sodium level	0.697	0.04	17.254	< 0.001	

HTS = hypertonic saline, OR = odds ratio.