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ORIGINAL WORK

Safety and Effect on Intracranial Pressure of 3% Hypertonic Saline Bolus Via Peripheral Intravenous Catheter for Neurological Emergencies

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Abstract

Background: Elevated intracranial pressure (ICP) is a neurological emergency in patients with acute brain injuries. Such a state requires immediate and effective interventions to prevent potential neurological deterioration. Current clinical guidelines recommend hypertonic saline (HTS) and mannitol as first-line therapeutic agents. Notably, HTS is conventionally administered through central venous catheters (CVCs), which may introduce delays in treatment due to the complexities associated with CVC placement. These delays can critically affect patient outcomes, necessitating the exploration of more rapid therapeutic avenues. This study aimed to investigate the safety and effect on ICP of administering rapid boluses of 3% HTS via peripheral intravenous (PIV) catheters.

Methods: A retrospective cohort study was performed on patients admitted to Sisters of Saint Mary Health Saint Louis University Hospital from March 2019 to September 2022 who received at least one 3% HTS bolus via PIV at a rate of 999 mL/hour for neurological emergencies. Outcomes assessed included complications related to 3% HTS bolus and its effect on ICP.

Results: Of 216 3% HTS boluses administered in 124 patients, complications occurred in 8 administrations (3.7%). Pain at the injection site (4 administrations; 1.9%) and thrombophlebitis (3 administrations; 1.4%) were most common. The median ICP reduced by 6 mm Hg after 3% HTS bolus administration ($p < 0.001$).

Conclusions: Rapid bolus administration of 3% HTS via PIV catheters presents itself as a relatively safe approach to treat neurological emergencies. Its implementation could provide an invaluable alternative to the traditional CVC-based administration, potentially minimizing CVC-associated complications and expediting life-saving interventions for patients with neurological emergencies, especially in the field and emergency department settings.

Keywords: 3% hypertonic saline, Peripheral intravenous catheter, Neurological emergencies, Safety, Intracranial pressure

Introduction

Signs and symptoms of elevated intracranial pressure (ICP) in patients with acute brain injury are considered neurological emergencies that require immediate recognition and treatment to prevent progression to cerebral ischemia, brain herniation, and death. Hyperosmolar agents, such as mannitol and hypertonic saline (HTS), are considered first-line therapies for the treatment of elevated ICP in current guidelines [1–4]. These agents may rapidly reduce brain volume and ICP in patients with cerebral edema by creating an osmolar gradient, facilitating fluids shift out of extravascular space [5].

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Further mechanisms of HTS include direct vasodilation, intravascular volume expansion, blood pressure and cardiac output augmentation, and potential neurochemical and immune-modulating effects [6]. Mannitol and HTS were compared in several randomized trials of patients with elevated ICP; meta-analyses of these trials found that HTS may have greater effect in managing elevated ICP, potentially improve cerebral perfusion, and avoid the unwanted side effects of mannitol, such as dehydration (secondary to its potent diuretic effect), rebound intracranial hypertension, and risk of precipitation during administration [7].

Although there was no robust evidence to compare the effectiveness of symptom-based bolus and continuous infusion of HTS in elevated ICP, the current guideline favors symptom-based bolus doses of HTS as a first-line intervention, along with other medical and surgical interventions for elevated ICP [1]. Bolus administration of HTS has become more favored because of its rapid effect and more transient increase in serum sodium levels [8]. Additionally, a prospective clinical trial reported an increased frequency of elevated ICP after stopping continuous HTS infusion, which was attributed to accumulated organic osmolytes related to higher overall increases in serum sodium levels [9]. Studies have shown the effect of HTS in patients with elevated ICP at various concentrations ranging from 1.8 to 23.4% [10–14]. However, data supporting the superiority of the various HTS concentrations are still lacking [1]. Traditionally, a central venous catheter (CVC) has been the preferred route of administration of 3% HTS. The American Society for Parenteral and Enteral Nutrition's recommendation of using a CVC for parenteral nutrition with osmolality above 900 mOsm/L solidified this practice in the past years given the high osmolality of 3% HTS (1026 mOsm/L) [15]. Additionally, because of its direct vasodilatory effects, there remain concerns that rapid administration may result in hypotension, bradycardia, or hemodynamic collapse [6]. However, it is well reported in the literature that CVC use is associated with complications that are both costly and carry their own risk of morbidity and mortality [16]. Furthermore, CVC placement is time consuming and requires trained personnel, which may delay administration of life-saving interventions, compromising patient care and worsening outcomes.

This has led to an increased interest in 3% HTS administration through a peripheral intravenous (PIV) catheter. Several prospective and retrospective studies have investigated the safety profile of 3% HTS administration via PIV catheters and have demonstrated that the complications were relatively minimal [17–21]. However, most of the studies enrolled patients with heterogenous indications for 3% HTS, and most of them received it at a slower infusion rate (< 100 mL/hour) with a prolonged infusion time (> 6 h) [22]. Recently, the safety of 3% HTS bolus via PIV catheter was established in a single-center retrospective study [16]. The purpose of this study is to describe the safety and effect on ICP of rapid bolus administration (at a rate of 999 mL/hour) of 3% HTS via PIV catheters for neurological emergencies.

Methods

Study Design and Setting

We conducted a retrospective single-center descriptive cohort study involving all patients admitted to Sisters of Saint Mary Health Saint Louis University Hospital between March 2019 and September 2022. Patients were included if they were 18 years or older and received at least one 3% HTS bolus via a PIV catheter at a rate of 999 mL/hour for neurological emergencies. It is our institutional protocol to always maintain two 18- or 20-gauge PIV catheters in any patients admitted to the intensive care unit. Patients were excluded if they met any of the following criteria: (1) presence of CVC during the period of 3% HTS administration, (2) continuous infusion of 3% HTS at a rate other than 999 mL/hour, and (3) administration of 3% HTS for indications other than neurological emergencies. The study was approved by our institutional review board (ID 33607), and formal consent was waived. This article was prepared following the Strengthening the Reporting of Observational Studies in Epidemiology guideline [23].

Data Extraction

Baseline demographics, including age, sex, and race, were extracted from the electronic medical records (EMRs). We also collected clinical information, such as primary diagnosis, clinical scales based on primary diagnosis at presentation, any cranial procedures during hospitalization, and the quantity and frequency of 3% HTS boluses. The Glasgow Coma Scale score was recorded in all patients enrolled in the study; the National Institute of Health Stroke Scale score was recorded only in patients with acute ischemic stroke; the intracerebral hemorrhage (ICH) score was documented only in patients with ICH; the Hunt and Hess scale and modified Fisher scale scores were recorded in patients with aneurysmal subarachnoid hemorrhage.

To assess safety outcomes, we recorded all complications related to 3% HTS bolus, including pain at the injection site, thrombophlebitis, vein thrombosis, and extravasation. Physiological data, such as ICP and mean arterial pressure (MAP), were regularly documented every hour per the nursing care protocol. We obtained the closest documented MAP before and after 3% HTS bolus administration to assess blood pressure changes

associated with bolus administration. Hypotension was defined as an MAP < 65 mm Hg or the new initiation or up-titration of vasopressors. Effect on ICP was determined by the change in ICP after 3% HTS bolus administration. Changes in serum sodium levels, chloride levels, and osmolality after 3% HTS bolus administration were also extracted. The laboratory tests were regularly drawn every four hours when the patients started to receive 3% HTS. Outcomes at discharge were represented by discharge disposition and the need for a tracheostomy and/or a percutaneous endoscopic gastrostomy tube.

Statistical Analysis

Descriptive statistics were performed to report proportions for categorical variables. For continuous variables, we calculated medians with interquartile ranges (IQRs) and means with standard deviations based on data distribution. Statistical inferences were conducted using the Mann–Whitney *U*-test and paired *t*-test for continuous variables, depending on their distribution. A two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 27.

Results

Of the 241 patients screened, 124 patients, who received a total of 216 administrations of 3% HTS boluses, met the inclusion criteria (Fig. 1). The most common reason for exclusion was presence of a CVC ($n = 84$), followed by an infusion rate < 999 mL/hour ($n = 21$) and indications other than elevated ICP ($n = 12$) (Fig. 1). Baseline patient characteristics are presented in Table 1. The mean age was 56.9 ± 18.7 years, 62.9% of patients were male,

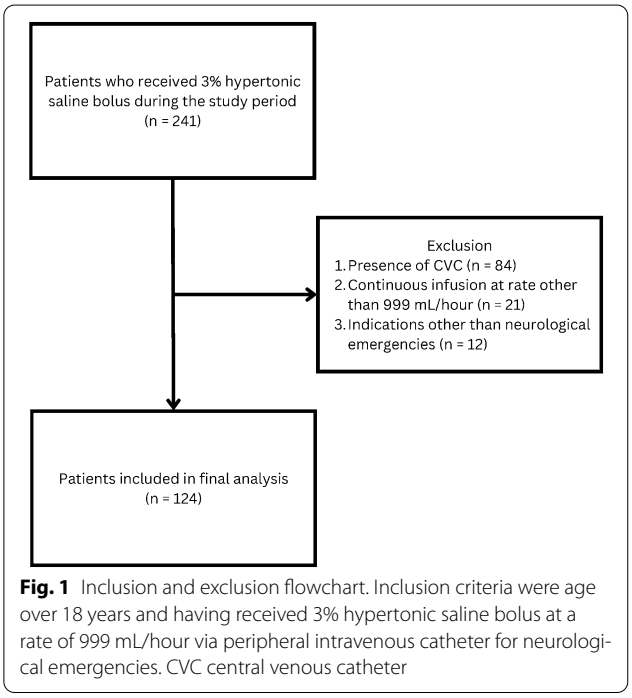

Fig. 1 Inclusion and exclusion flowchart. Inclusion criteria were age over 18 years and having received 3% hypertonic saline bolus at a rate of 999 mL/hour via peripheral intravenous catheter for neurological emergencies. CVC central venous catheter

Table 1 Demographic and clinical characteristics of study population

	Value
Sex	
Male, *n* (%)	78 (62.9)
Age, years, mean (± SD)	56.9 (± 18.7)
Race, *n* (%)	
Caucasian	68 (54.8)
African American	44 (35.5)
Other[a]	12 (9.7)
Primary diagnosis, *n* (%)	
ICH	47 (37.9)
AIS	36 (29.0)
TBI	34 (27.4)
aSAH	4 (3.2)
Others[b]	3 (2.4)
Clinical scales on admission, median (IQR)[c]	
ICH score	3 (2–4)
NIHSS score	17 (11–26)
GCS score	7 (4–14)
HH score	3 (1–5)
mF score	4 (4–4)
Cranial procedures, *n* (%)	
EVD	46 (37.1)
Decompressive surgery[d]	27 (21.8)
Need for tracheostomy	25 (20.2)
Need for PEG tube	30 (24.2)
Discharge destination, *n* (%)	
Home	7 (5.6)
Acute rehabilitation facility	31 (25.0)
Skilled nursing facility	7 (5.6)
Long-term acute care hospital	11 (8.9)
Death/comfort care	68 (54.8)
Frequency of 3% HTS bolus, median (IQR)	1 (1–2)
Quantity of 3% HTS received in mL, median (IQR)	250 (250–250)

[a] Included Hispanic, Asian, and American Indian

[b] Included anoxic brain injury, central nervous system infection, and brain tumor

[c] All patients had a GCS score documented. The ICH score is specific to patients with ICH, the NIHSS score is specific to patients with ischemic stroke, and the HH and mF scores are specific to patients with aSAH

[d] Included decompressive hemicraniectomy, decompressive bifrontal craniectomy, suboccipital craniectomy, and craniotomy

AIS acute ischemic stroke, *aSAH* aneurysmal subarachnoid hemorrhage, *EVD* external ventricular drain, *GCS* Glasgow Coma Scale, *HH* Hunt and Hess, *HTS* hypertonic saline, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *mF* modified Fisher scale, *NIHSS* National Institute of Health Stroke Scale, *PEG* percutaneous endoscopic gastrostomy, *TBI* traumatic brain injury

and the majority were White (54.8%). The most common primary diagnoses on admission were ICH (37.9%) and acute ischemic stroke (29%), followed by traumatic brain injury (27.4%). The median ICH score was 3 (IQR 2–4), the median National Institute of Health Stroke Scale score was 17 (IQR 11–26), and the median Glasgow Coma Scale score on admission was 7 (IQR 4–14). All 3% HTS boluses were administrated at 999 mL/hour in our study. The median quantity of each bolus was 250 (IQR 250–250) mL. Forty-two patients (33.9%) also received mannitol for neurological emergencies in addition to 3% HTS. The median frequency of 3% HTS bolus administration was 1 (IQR 1–2). Forty-six patients (37.1%) received external ventricular drain placement for cerebrospinal fluid diversion and ICP monitoring. A total of 27 patients (21.8%) underwent a decompressive surgery appropriate to the primary diagnosis to relieve elevated ICP. Twenty-five (20.2%) and 30 (24.2%) patients had a tracheostomy and percutaneous endoscopic gastrostomy tube placement, respectively, at discharge (Table 1). A total of 68 patients (54.8%) died or were transitioned to comfort care at hospital discharge, whereas 7 (5.6%) and 31 (25.0%) patients were discharged to home or to an acute rehabilitation facility, respectively (Table 1).

A total of eight (3.7%) administrations of 3% HTS were associated with at least one complication. Following the administration of a single 3% HTS bolus, one patient developed vein thrombosis, another experienced thrombophlebitis, and one reported pain at the infusion site. In patients who received more than one bolus of 3% HTS, one developed vein thrombosis following three administrations, whereas another experienced thrombophlebitis after two administrations. One patient developed thrombophlebitis, pain, and extravasation after three administrations, and two patients reported pain at the site of administration following administration of three and five boluses, respectively (Table 2). For those patients with reported reactions, the most common gauge of PIV catheter used was the 18-gauge catheter, and the most common placement location was the forearm (Supplementary Table 1).

There were 75 pairs of before and after 3% HTS bolus ICP values documented in the EMR (Table 3). The median ICP prior to 3% HTS bolus administration was 18.4 (IQR 11–23) mm Hg, and the median ICP after 3% HTS bolus administration was 13.8 (IQR 7.75–18) mm Hg, which was statistically significant ($p < 0.001$). After we excluded patients who received mannitol at any time point, the median ICP decreased from 17.5 to 11.5 mm Hg after 3% HTS bolus administration ($p < 0.001$). The mean MAP also rose from 91.2 to 94.3 mm Hg after 3% HTS bolus administration ($p = 0.03$). The mean values of sodium, chloride and serum osmolality increased by 3.2 mEq/L, 5.5 mEq/L, and 7.1 mOsm/kg, respectively, after each 3% HTS bolus administration ($p < 0.001$).

Table 2 Safety outcomes following 3% hypertonic saline bolus administration

Complications ($N = 216$ boluses)	*n* (%)
Any complication with hypertonic saline bolus[a]	8 (3.7)
Pain	4 (1.9)
Thrombophlebitis	3 (1.4)
Vein thrombosis	2 (0.9)
Extravasation	1 (0.5)

[a] Some patients had more than one complication associated with a single bolus of 3% hypertonic saline

Discussion

Our study demonstrates that rapid bolus administration at a rate of 999 mL/hour via either an 18- or 20-gauge PIV catheter is relatively safe. Of 216 bolus administrations of 3% HTS peripherally, complications only occurred in 8 administrations (3.7%). No severe complications, such as hypotension, were identified with rapid bolus administrations of 3% HTS via PIV catheters. Our

Table 3 Change in physiological and laboratory values before and after 3% hypertonic saline bolus administration

Physiological and laboratory variables	Before	After	*p* value
ICP, median (IQR), mm Hg[a]	18.4 (11–23)	13.8 (7.75–18)	< 0.001
ICP, median (IQR), mm Hg[b]	17.5 (9.75–22.25)	11.5 (7.75–18)	< 0.001
MAP, mean ± SD, mm Hg	91.2 ± 20.6	94.3 ± 24.3	0.03
Sodium, mean ± SD, mEq/L	141.4 ± 5.8	144.6 ± 5.6	< 0.001
Chloride, mean ± SD, mEq/L	108.2 ± 7.9	113.7 ± 6.6	< 0.001
Osmolality, mean ± SD, mOsm/kg	298.0 ± 14.3	305.1 ± 13.5	< 0.001
Creatinine, median (IQR), mg/dL	1.0 (1.0–1.27)	0.93 (0.68–1.33)	0.58

[a] There were 75 pairs of ICP values in the before and after hypertonic saline bolus group

[b] There were 64 pairs of ICP values in the before and after hypertonic saline bolus group after exclusion of patients who received mannitol at any time point

ICP intracranial pressure, *IQR* interquartile range, *MAP* mean arterial pressure

study also demonstrated the effect of peripheral 3% HTS bolus administration on ICP reduction. In our study, the median ICP decreased by 6 mm Hg after 3% HTS bolus was administered ($p < 0.001$). Serum sodium levels, chloride levels, and osmolality also rose as anticipated, in accordance with each bolus administration ($p < 0.001$).

There are limited studies investigating the safety of 3% HTS bolus administration via PIV catheters. Most of the existing literature reported patients receiving 3% HTS via PIV catheters at a lower infusion rate (< 100 mL/hour) with a prolonged infusion time (> 6 h), and infusion-related complication rates ranged from 2.9% to 10.7% [22]. One study comparing 3% HTS and mannitol boluses via PIV catheters for neurological emergencies did not identify any bolus-related complications, but notably the authors did not report bolus rates and identified only extravasation as the sole complication of interest [21]. Seven (8.2%) patients who received 3% HTS boluses also developed acute kidney injury within the next 48 h [21]. Another study reported use of 3% HTS boluses via PIV catheters at a median rate of 760 mL/hour for neurological emergencies [16]. They did not observe any adverse effects at the site of infusion; however, four patients (12.5%) experienced hypotension (defined by the authors as a systolic blood pressure < 100 mm Hg) while receiving the 3% HTS bolus [16]. In comparison to existing literature, all patients included in our cohort received 3% HTS bolus at the rate of 999 mL/hour via an 18- or 20-gauge PIV catheter for neurological emergencies, and bolus-related complications occurred in 3.7% of 3% HTS bolus administrations, which aligns with the complication risk reported in the existing literature. Interestingly, the mean MAP in our cohort increased by 3.1 mm Hg ($p = 0.03$) after 3% HTS bolus administration, which likely represented the volume expansion effect of 3% HTS [6].

This study evaluated the safety and effect on ICP of 3% HTS administered at a rate of 999 mL/hour via PIV catheters, which provided valuable data to support its application in the setting of neurological emergencies. Although there were no studies that directly compared the safety or effect on ICP of centrally administered 3% HTS and that which is given peripherally, it is well reported in the literature that CVCs are associated with costly complications that carry morbidity and mortality risks, regardless of the infused solution [16]. Our data may assuredly allow institutions to consider alteration of restrictions on administration of 3% HTS in neurological emergencies when bolus of hypertonic solution is recommended according to the most recent practice guideline [1]. Although there is also rising interest in peripheral administration of 23.4% HTS for neurological emergencies, it is not free from serious adverse events, and most institutions still mandate the use of 23.4% HTS via CVC by slow push over 10 to 15 min [5, 24]. The use of equiosmolar 3% HTS boluses for neurological emergencies might be a more viable alternative to 23.4% HTS when it is unavailable or unsafe to administer, especially in the field or emergency department, but further studies directly comparing the effect on ICP reduction of an equiosmolar dose of 3% HTS with that of 23.4% HTS are warranted (30 mL of 23.4% HTS has a similar osmolar load compared to 250 mL of 3% HTS).

There are several inherent limitations to our study. First is the retrospective, noncomparative, and single-center nature of its design. We also relied heavily on the documentation of adverse events in the EMR, and thus it is likely that minor complications, such as injection site pain or phlebitis, may have been underreported because of patients' consciousness. However, our robust electronic safety event reporting system lends confidence that major events would be captured in review. Because this was a retrospective analysis of a hospital-wide medication administration policy change, it lacks a comparison arm. At our institution, nurses use the largest PIV catheter in the location with the greatest blood flow; for example, the 18-gauge PIV catheter in the antecubital fossa will be preferred over a 20-gauge line in the hand. When a bolus is given, nurses run it through a dedicated PIV site. If an infusion site reaction is identified, the nursing staff will move the infusion to another PIV site, notify the physician team, and document the reaction and site of infusion in the EMR. However, because of the low rate of complications, for the majority of administrations, we were unable to specify PIV site or gauge used for bolus administration. To ensure all patients in our analysis received 3% HTS boluses via PIV catheters, we excluded all who had a CVC in place during the period when 3% HTS boluses were administered. By doing this, we also ensured exclusion of patients who received 23.4% HTS because it can only be administered via CVC per our institution protocol. We recognize that this exclusion may have limited the severity of our patient population. Additionally, some PIV catheters may have had additional medications administered before or after the 3% HTS boluses, potentially confounding our complication analysis. We sought to include all neurologically critically ill patients and because of their heterogenous disease processes, we lacked ICP data for every single patient.

Conclusions

This study examined the safety and effect on ICP of peripheral 3% HTS boluses for neurological emergencies. Our findings emphasize the low risks of peripheral 3% HTS boluses at a rate of 999 mL/hour and their effect in lowering ICP. There were no hypotension events identified after 3% HTS bolus administration. Administration

of 3% HTS boluses via PIV catheters at a rate of 999 mL/hour may be considered a safe rescue in the setting of neurological emergencies. Further studies are warranted to compare the safety and effect on ICP of 3% HTS and 23.4% HTS administration in neurological emergencies.

Supplementary Information
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Author Contributions
FK: acquisition and interpretation of data, draft of manuscript; AH: acquisition and interpretation of data, draft of manuscript; KC: analysis and interpretation of data, revision of manuscript critically for important intellectual content; JB: conceptualization of study design, interpretation of data, revision of manuscript critically for important intellectual content; FW: conceptualization of study design, analysis and interpretation of data, revision of manuscript critically for important intellectual content.

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None.

Conflicts of Interest
The authors declare no conflicts of interest.

Ethical Approval/Informed Consent
This study was approved by Saint Louis University Institutional Review Board, and informed consent was waived given the nature of the retrospective study.

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