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SAFETY OF PERIPHERAL LINE ADMINISTRATION OF 3% HYPERTONIC SALINE AND MANNITOL IN THE EMERGENCY DEPARTMENT

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□ **Abstract—Background: Hypertonic saline (HTS) and mannitol are frequently utilized in the emergency department (ED) to manage elevations in intracranial pressure (ICP). Objective: The objective of this study was to compare the incidence of extravasation injury when HTS or mannitol was administered via peripheral i.v. line (PIV). Methods: This retrospective cohort study evaluated adult and pediatric patients given either 3% HTS or mannitol via PIV while in the ED. The primary outcome was extravasation incidence. Results: One hundred and ninety-two patients were included, of which 85 (44%) received HTS and 107 (56%) received mannitol. Patients who received HTS were younger (27.5 ± 24.3 years vs. 53.9 ± 22.3 years; $p < 0.001$); 55.3% of patients given HTS received it for traumatic brain injury (TBI) versus 38.3% of patients given mannitol ($p = 0.021$); and 44.9% of patients given mannitol received it for intracerebral hemorrhage versus 21.2% of patients given HTS ($p = 0.001$). There was no incidence of extravasation in either group. Patients who received HTS had lower ICP measurement 24 h post admission (2.107 ± 5.5 mm Hg vs. 4.236 ± 8.1 mm Hg; $p = 0.047$) and higher Glasgow Coma Scale (GCS) score upon discharge (GCS 14; interquartile range [IQR] 3–15 vs. GCS 3; IQR 3–14.2; $p = 0.004$). In-hospital mortality was higher in the mannitol group (54.7% vs. 32.9%; $p = 0.003$). Duration of mechanical ventilation was shorter in those patients who received HTS (1 day; IQR 0–56 days vs. 2 days; IQR 0–56 days; $p = 0.023$). Conclusions: There were no incidences of extravasation among patients given 3% HTS or mannitol. Clinicians should reconsider recommendations to restrict HTS or mannitol to central lines.** **© 2018 Elsevier Inc. All rights reserved.**

□ **Keywords—hypertonic saline; mannitol; intravenous; emergency department; medication safety; extravasation**

INTRODUCTION

HTS and mannitol have been increasingly utilized in the emergency department to manage elevated intracranial pressure (ICP) (1). Studies comparing the efficacy of these agents suggest a similar impact on ICP and clinical outcomes (2). While there are numerous studies comparing the efficacy of mannitol and HTS, there is limited literature comparing the safety, specifically, adverse events related to tissue injury (3–6). Infusion-related adverse events (e.g., extravasation, phlebitis, thrombophlebitis) have been reported in 0–10.7% of patients receiving HTS via peripheral line (3–6). These conflicting reports may lead to confusion about the safety of HTS that causes delays in administration. Despite also being a hyperosmolar solution, extravasation, or other infusion-related events, have not been reported in patients receiving mannitol. To assist

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providers with decisions regarding the need to delay hyperosmolar administration, we sought to evaluate the safety of HTS and mannitol via PIV in the ED.

MATERIALS AND METHODS

A retrospective, single-center, cohort study was conducted at Loma Linda University Medical Center (LLUMC), which includes a 797-bed adult and pediatric (younger than 18 years old) teaching hospital designated as a Level I trauma center. LLUMC contains a 65-bed adult and pediatric ED with 76,000 visits per year. This study included adult and pediatric patients given either 3% HTS or mannitol 20% or 25% via PIV while in the ED at LLUMC between April 1, 2013 and September 30, 2015. Patients were initially identified if they received medication orders for any of the previously listed hyperosmolar agents in the ED during the study period. In the ED at LLUMC, bolus PIV administration of 3% HTS and mannitol is permitted during medical emergencies for adult and pediatric patients. HTS is usually administered as a 5 mL/kg bolus, while mannitol is administered as a 1 g/kg bolus. Bolus doses can be repeated at the discretion of the treating health care professional. Health care professionals can also order HTS or mannitol as continuous infusions, although bolus dosing is preferred due to more rapid administration. Patients were excluded if they received both HTS and mannitol via the same PIV, were pregnant, if HTS or mannitol was ordered but not administered, or if they received mannitol for hemodialysis. Patients receiving both agents via the same PIV were excluded to ensure any extravasation event could be clearly attributed to either HTS or mannitol. E.M. screened for inclusion/exclusion criteria. The primary outcome was extravasation incidence, which was defined as any inadvertent administration of solution into the surrounding tissue instead of the intended PIV pathway and identified via health care professional progress notes in the electronic medical record. Secondary outcomes included severity of infusion-related injury per Infusion Nurses Society definitions, incidence of hypokalemia (<3.5 mmol/L), hyperchloremia (>110 mmol/L), and hypernatremia (>155 mmol/L), incidence of acute kidney injury (AKI) within 48 h of admission per KDIGO (Kidney Disease: Improving Global Outcomes) criteria, intracranial pressure (ICP) initially and 24 h post treatment, duration of mechanical ventilation, intensive care unit (ICU) and hospital length of stay (LOS), in-hospital mortality, and Glasgow Coma Scale (GCS) score at discharge (7,8).

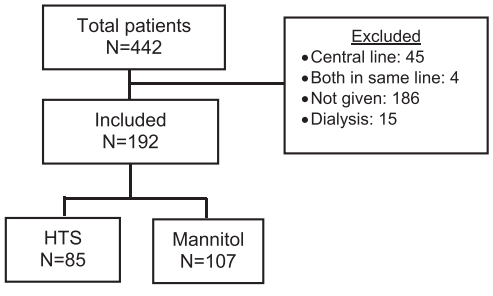
Data were collected from the patient's medical records by E.M. and included age, sex, body mass index, laboratory results, medical history, home medication use, admission location, physical and neurologic assessment results, indication for HTS or mannitol, information related to ED medication administration, duration of mechanical ventilation, and ICU and hospital LOS. Infusion-related injury severity was determined by the health care professional's progress notes. Only electrolyte abnormalities within 24 h of admission were considered for analysis. SF and KM randomly audited collected data to ensure accuracy. Authors were not blinded to the study question. Data were collected using Microsoft Excel (Microsoft Office Professional Plus 2016; Microsoft, Redmond, WA). Final Institutional Review Board approval, number 5170428, was obtained on January 5, 2018.

A sample size of 146 patients was estimated to detect a 10% difference in extravasation incidence between HTS and mannitol based on literature reporting infusion-related adverse events in nearly 11% of those receiving HTS, and our hypothesis that these events would occur in 1% of those given mannitol (power 0.8, $\alpha = 0.05$) (4). Descriptive statistics for continuous variables were presented using the mean with standard deviation if the values were normally distributed and median with IQR if not normally distributed. Categorical variables were presented with number and percentage. Continuous variables were compared using the two-independent samples *t*-test when assumptions of parametric tests were met, while the Mann–Whitney test was used to compare variables when assumptions of parametric tests were not met. χ^2 Tests were used to assess the association of the categorical variables between groups. When assumptions of χ^2 were not met, Fisher's exact tests were used. Significance was set at an α of 0.05. Statistical analysis was performed by K.B. and K.M. using SPSS Statistics software (version 25.0, IBM Corp, Armonk, NY).

RESULTS

Patient Demographics

Four hundred and forty-two patients were initially screened for the study. After elimination based on exclusion criteria, 192 patients were included for analysis (Figure 1). Forty-nine (26%) were pediatric patients.



HTS = hypertonic saline.

Figure 1. Study flow diagram. HTS = hypertonic saline.

Table 1. Patient Demographic Characteristics

Characteristics	HTS (n = 85)	Mannitol (n = 107)	*p* Value
Age, y, mean ± SD	27.5 ± 24.3	53.9 ± 22.3	<0.001
Female, n (%)	35 (41.2)	40 (37.4)	0.463
Weight, kg, mean ± SD	58.6 ± 34	76.6 ± 22.4	<0.001
BMI, mean ± SD	25.5 ± 10.5	28.3 ± 7.9	0.059
Admission GCS, median (IQR)	7 (3–15)	5 (3–15)	0.597
Altered at admission, n (%)	83 (97.6)	95 (88.8)	0.023
Hypotensive at admission, n (%)	10 (11.8)	11 (9.9)	0.677
Diabetes, n (%)	14 (16.5)	17 (15.9)	0.826
Peripheral vascular disease, n (%)	3 (3.5)	7 (6.5)	0.519
i.v. drug use, n (%)	2 (2.4)	8 (7.5)	0.191
ESRD, n (%)	0 (0)	7 (6.5)	0.020
Obesity, n (%)	10 (12.3)	19 (20.2)	0.182
Anticoagulant use at home, n (%)	3 (3.5)	10 (9.3)	0.100
Antiplatelet use at home, n (%)	8 (9.4)	19 (17.8)	0.098
Mechanical ventilation required, n (%)	60 (70.6)	88 (82.2)	0.056
Indication, n (%)			
AIS	2 (2.3)	3 (2.8)	1
TBI	47 (55.3)	41 (38.3)	0.021
ICH	18 (21.2)	48 (44.9)	0.001
Other	18 (21.2)	15 (14)	0.248

AIS = acute ischemic stroke; BMI = body mass index; ESRD = end-stage renal disease; GCS = Glasgow Coma Scale; HTS = hypertonic saline; ICH = intracerebral hemorrhage; SD = standard deviation; TBI = traumatic brain injury.

Eighty-five (44%) received HTS and 107 (56%) received mannitol. HTS was used mostly for TBI, while mannitol was predominantly used for intracerebral hemorrhage (Table 1). At baseline, patients receiving HTS were younger (27.5 ± 24.3 years vs. 53.9 ± 22.3 years; $p < 0.001$), had lower weight (58.6 ± 34 kg vs. 76.6 ± 22.4 kg; $p < 0.001$), had less end-stage renal disease (0% vs. 6.5%; $p = 0.02$), and more often presented with altered mental status (97.6% vs. 88.8%; $p = 0.023$) compared to patients receiving mannitol. All other baseline characteristics were similar between groups (Table 1). Most patients received bolus dosing of HTS or mannitol (Table 2). Mannitol 25% was the concentration most often utilized (Table 2).

Outcomes

In terms of the primary outcome, there was no incidence of extravasation observed in either group (0% vs. 0%; $p > 0.999$). There were no differences in safety-related secondary outcomes, including electrolyte abnormalities or incidence of AKI between groups (Table 3). In terms of efficacy-related secondary outcomes, patients receiving HTS had lower ICP 24 h post admission (2.107 ± 5.5 mm Hg vs. 4.236 ± 8.1 mm Hg; $p = 0.047$) and had a higher GCS at discharge (GCS 14; IQR 3–15 vs. GCS 3; IQR 3–14.2; $p = 0.004$). Duration of mechanical ventilation was shorter in those who received HTS (1 day; IQR 0–56 days vs. 2 days; IQR 0–56 days; $p = 0.023$). In-hospital mortality was higher in patients receiving mannitol (54.7% vs. 32.9%; $p = 0.003$). There were no differences in expansion of hematoma 24 h after admission, ICU LOS, or hospital LOS (Table 4).

DISCUSSION

Concern for extravasation-induced tissue injury has led to recommendations not to administer solutions exceeding 900 mOsmol/L via PIV (9). Three-percent HTS has an osmolarity of 1,027 mOsmol/L compared to 1,098 mOsmol/L for 20% mannitol and 1,372 mOsmol/L for 25% mannitol (10–12). Based on osmolarity alone, HTS and mannitol 20% or 25% should be reserved for central lines. There have been several studies evaluating the safety of HTS via PIV in adult patients (3–5). Infusion-related complication rates have ranged from 6.1% to 10.7%; however, none of these complications resulted in serious tissue injury

Table 2. Dosing Characteristics of Hypertonic Saline and Mannitol

Characteristics	HTS (n = 85)	Mannitol (n = 107)
Bolus given, n (%)	78 (91.8)	106 (99.1)
Continuous infusion given, n (%)	7 (8.2)	1 (0.9)
Dose, mean ± SD		
mL	282.7 ± 183.3	NA
mL/kg	6 ± 7.98	NA
g	NA	75.7 ± 42.6
g/kg	NA	0.97 ± 0.49
Mannitol concentration, n (%)		
20%	NA	17 (15.9)
25%	NA	90 (84.1)

HTS = hypertonic saline; NA = not applicable; SD = standard deviation.

Table 3. Safety-Related Outcomes

Outcomes	HTS, n (%) (n = 85)	Mannitol, n (%) (n = 107)	*p* Value
Extravasation event	0 (0)	0 (0)	>0.999
Electrolyte abnormality	40 (47.6)	55 (52.4)	0.515
Hypokalemia	21 (24.7)	27 (25.7)	0.874
Hyperchloremia	33 (38.8)	40 (38.1)	0.918
Hypernatremia	7 (8.2)	14 (13.3)	0.265
AKI	7 (8.2)	6 (5.7)	0.482

AKI = acute kidney injury per KDIGO (Kidney Disease: Improving Global Outcomes) criteria; HTS = hypertonic saline.

(3–5). One study that evaluated pediatric patients receiving HTS via PIV reported no infusion-related complications (6). Based on our findings, and those of previous studies, infusion-related complications are infrequent, mild in nature, and should not justify delay of hyperosmolar therapy during medical emergencies.

Although there were no differences in patients receiving HTS or mannitol with regard to the primary outcome, there were several differences in secondary outcomes. Patients receiving HTS had lower ICP 24 h after admission, higher GCS at discharge, lower in-hospital mortality, and shorter duration of mechanical ventilation. The numerous differences in demographics likely explain these findings. Patients receiving HTS were younger, had less history of end stage renal disease (ESRD), and had trends towards higher admission GCS, less anticoagulant use, and less antiplatelet use. Most patients receiving HTS received it for TBI, while most patients receiving mannitol received it for intracerebral hemorrhage. These differences suggest that patients receiving mannitol had more comorbidities and a poorer prognosis at baseline compared to patients receiving HTS. Results of this study should not be used to justify clinical superiority of HTS.

Limitations

This study had several limitations. First, we included a diverse set of patients that included adults and pediatrics. These patients had different indications for HTS or mannitol and differences in baseline characteristics, such as age and comorbidities. Our study focused on the safety of HTS and mannitol via PIV. Because we focused on this outcome, we thought it was appropriate to study a diverse set of patients to evaluate whether a specific type of patient was at risk for extravasation or other adverse events. Second, this study was a retrospective chart review. Differences in secondary outcomes, such as duration of mechanical ventilation or mortality, could have been due to measured or unmeasured confounders rather than treatment with HTS or mannitol. These findings regarding clinical efficacy should not be used to recommend HTS over mannitol. Third, health care professional progress notes were used to determine whether extravasation or other infusion-related events occurred. We were unable to determine whether extravasation occurred but was not documented. Fourth, our study may have been underpowered to compare differences in extravasation events between those receiving HTS and mannitol. As described previously, studies have documented infusion-related complication rates in 0–10.7% of patients (3–6). We expected a 10% difference in extravasation events between HTS and mannitol. If this event rate is < 10%, it could explain why we found no incidence of extravasation in either group. Fifth, we did not include pregnant patients, so our findings may not apply to that patient population. Sixth, authors collecting data were not blinded to the study question. Study data were primarily collected by one author and

Table 4. Efficacy-Related Outcomes

Outcomes	HTS (n = 85)	Mannitol (n = 1 07)	*p* Value
ICP 24 h post admission, mm Hg, mean ± SD	2.107 ± 5.5	4.236 ± 8.1	0.047
GCS at admission, median (IQR)	7 (3–10)	5 (3–12)	0.555
GCS at discharge, median (IQR)	14 (3–15)	3 (3–14.2)	0.004
In-hospital mortality, mean ± SD	28 (32.9)	58 (54.7)	0.003
Expansion of hematoma 24 h post admission, n (%)	6 (7.2)	11 (10.4)	0.453
Duration of mechanical ventilation, d, median, (IQR)	1 (0–56)	2 (0–56)	0.023
ICU LOS, d, median (IQR)	4 (0–56)	4 (0–56)	0.657
Hospital LOS, d, median (IQR)	5 (2–10.5)	5.5 (1–15)	0.881

GCS = Glasgow Coma Scale; HTS = hypertonic saline; ICP = intracranial pressure; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay.

audited by the others. Ideally, this should have controlled for bias during data collection. Finally, most patients received HTS or mannitol as an i.v. bolus, meaning results do not reflect the safety of prolonged administration strategies, such as continuous i.v. infusion.

CONCLUSIONS

We found that there were no incidences of extravasation among adult or pediatric patients given 3% HTS or mannitol via PIV. Although this study was not designed to assess efficacy-related outcomes, and there were significant demographic differences between those receiving HTS or mannitol, patients that received HTS had lower in-hospital mortality, ICP 24 h post admission, shorter duration of mechanical ventilation, and higher discharge GCS. Clinicians should reconsider recommendations to restrict HTS or mannitol to central lines.

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ARTICLE SUMMARY

1. Why is this topic important?

Emergency and critical care physicians may face reluctance to administer hypertonic saline (HTS) through peripheral i.v. line (PIV) due to concern for extravasation and tissue injury.

2. What does this study attempt to show?

This study attempts to show that 3% HTS has similar safety to mannitol when administered through PIV.

3. What are the key findings?

Out of the total study population, none developed extravasation when given 3% HTS or mannitol through PIV.

4. How is patient care impacted?

Three percent HTS and mannitol can safely be administered through PIV in patients in need of urgent hyperosmolar therapy without central venous catheter placement.