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ORIGINAL WORK

Safety and Efficacy of 23.4% Sodium Chloride Administered via Peripheral Venous Access for the Treatment of Cerebral Herniation and Intracranial Pressure Elevation

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Abstract

Background: Sodium chloride (NaCl) 23.4% solution has been shown to reduce intracranial pressure (ICP) and reverse transtentorial herniation. A limitation of 23.4% NaCl is its high osmolarity (8008 mOsm/l) and the concern for tissue injury or necrosis following extravasation when administered via peripheral venous access. The use of this agent is therefore often limited to central venous or intraosseous routes of administration. Our objective was to evaluate the safety and efficacy of administration of 23.4% NaCl via peripheral venous access compared with administration via central venous access.

Methods: We reviewed pharmacy records to identify all administrations of 23.4% NaCl at our institution between December 2017 and February 2020. Medical records were then reviewed to identify complications, such as extravasation, soft tissue injury or necrosis, hypotension (mean arterial pressure less than 65 mm Hg), pulmonary edema, hemolysis, and osmotic demyelination. We also compared the change in physiological variables, such as ICP, mean arterial pressure, cerebral perfusion pressure, and heart rate, as well as laboratory values, such as sodium, chloride, bicarbonate, creatinine, and hemoglobin, following administration of 23.4% NaCl via the peripheral and central venous routes.

Results: We identified 299 administrations of 23.4% NaCl (242 central and 57 peripheral) in 141 patients during the study period. There was no documented occurrence of soft tissue injury or necrosis in any patient. One patient developed hypotension following central administration. Among the 38 patients with ICP monitoring at the time of drug administration, there was no significant difference in median ICP reduction (− 13 mm Hg [central] vs. − 24 mm Hg [peripheral], $p = 0.21$) or cerebral perfusion pressure augmentation (16 mm Hg [central] vs. 15 mm Hg [peripheral], $p = 0.87$) based on route of administration.

Conclusions: Peripheral venous administration of 23.4% NaCl is safe and achieves a reduction in ICP equivalent to that achieved by administration via central venous access.

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Introduction

Elevated intracranial pressure (ICP) from cerebral edema can occur following various forms of acute brain injury. Current guidelines for the management of cerebral edema and elevated ICP recommend the use of hyperosmolar therapy with either hypertonic saline or mannitol [1–3] Hypertonic saline (sodium chloride [NaCl]), commercially available in concentrations ranging from 3 to 23.4%, is highly effective in lowering ICP [1, 4–8]. Recent studies suggest hypertonic saline may achieve a more enduring and potent reduction in ICP than mannitol, and can effectively treat ICP elevations refractory to mannitol and hyperventilation [9, 10]. Hypertonic saline lacks many of the detrimental properties of mannitol, such as its potent diuretic effect (which may exacerbate preexisting hypovolemia), rebound intracranial hypertension, and the need for an in-line filter due to the risk of crystallization [11, 12]. Sodium chloride (NaCl) 23.4% solution is particularly advantageous because it is effective in reversing transtentorial herniation [4] and is available in compact 30-ml vials, more suitable for transport and storage than bags of saline. Although these advantages are relevant to a variety of settings, such as emergency department and prehospital use by emergency medical services, one specific benefit is that vials are more easily carried in backpacks by military medics performing tactical field care and tactical evacuation.

Concerns about the safety of use through peripheral venous access has, however, limited the use of 23.4% NaCl in these settings. When administered via peripheral venous access, extremely hyperosmolar agents, such as 23.4% NaCl, may result in thrombophlebitis, injection-site pain, and tissue injury or necrosis with extravasation [13]. Tissue injury occurs as a result of severe dehydration of surrounding tissue. The perceived risk of tissue injury has led to widespread restrictions on the route of administration of 23.4% NaCl (osmolarity 8008 mOsm/l) to central venous access only [6, 7, 14]. Cerebral herniation is a medical emergency, however, and may result in death or permanent neurological injury with any delay in treatment [15]. Central venous cannulation takes time and is associated with serious risks, such as pneumothorax, arterial cannulation, bleeding, and infection. As an alternative, emergent intraosseous administration of 23.4% NaCl has been described [14]. However, this route may also result in extravasation and tissue injury in addition to other serious adverse events, such as osteomyelitis [16]. Peripheral venous access is present or easily established in most patients with acute neurological emergencies and allows for immediate administration of the medication without delay or the need for expertise in central venous or intraosseous access. Several studies have demonstrated that administration of 3% NaCl via peripheral venous access is associated with a very low rate of significant complications [17, 18]. However, there are no published studies of the safety of use of 23.4% NaCl via peripheral venous access.

Because cerebral herniation is a time-sensitive neurological emergency, our institution revised its policy to permit the use of 23.4% NaCl via peripheral venous access when central venous access is unavailable. Our objective therefore was to evaluate the safety and efficacy of peripheral venous administration of 23.4% NaCl compared with central venous administration for the treatment of cerebral herniation and elevated ICP.

Methods

The institutional review board determined that this retrospective cohort study, with data obtained exclusively from chart review, was exempt from the need for approval. For this type of study, formal consent is not required. All adult patients (aged older than 18 years) who received 23.4% NaCl in the period from December 2017 to February 2020 were included and identified via pharmacy records, which include all instances of 23.4% NaCl use at our institution. Data extracted via chart review included demographics, diagnoses, physiological variables prior to and following the use of 23.4% NaCl, route of administration, dose administered, and the occurrence of complications. The occurrence of cerebral herniation was also extracted through review of the medical record. A diagnosis of cerebral herniation was made on the basis of new and otherwise unexplained symptoms of stupor, posturing, or pupillary asymmetry in combination with radiological evidence of a mass lesion or diffuse cerebral edema.

The primary objective of this study was to evaluate the safety of administration of 23.4% NaCl via peripheral compared with central venous access. Soft tissue complications related to peripheral venous administration included known extravasation, documentation of pain during injection, and signs of thrombophlebitis, cellulitis, and/or necrosis. Other complications included hypotension to mean arterial pressure (MAP) less than 65 mm Hg within 60 min of drug administration, drop in systolic blood pressure (SBP) by 20 mm Hg within 60 min of

drug administration, hemolysis, acute pulmonary edema, osmotic demyelination, and any other adverse event documented to be a consequence of administration of 23.4% NaCl. Skin and soft tissue complications, including thrombophlebitis and tissue injury, were routinely documented by nursing in designated areas of the electronic medical record. We reviewed medical records for soft tissue complications for the duration of the inpatient stay. Pulmonary edema as a complication of administration of 23.4% NaCl was defined as the new development of airspace or interstitial opacities on the radiograph or B lines on the lung ultrasound image, in conjunction with clinical respiratory deterioration in any form (increased oxygen requirement, increased work of breathing, tachypnea, or other), within 24 h of administration of the agent or acute worsening of existing radiographic abnormalities or clinical symptoms within this period. Osmotic demyelination was defined as neurological deterioration, particularly new bulbar symptoms, occurring at any time during the inpatient stay following administration of the agent, in conjunction with new hyperintense lesions observed in the brainstem or diencephalon on the magnetic resonance imaging scan consistent with demyelination. The sample size for analysis of safety outcomes (complications) included all administrations of the agent, including repeat administration in individual patients.

Our secondary objective was to evaluate the efficacy of peripheral versus central venous administration of 23.4% NaCl for the lowering of ICP and augmentation of cerebral perfusion pressure (CPP). To avoid error from multiple measurements, only the first administration of the agent per patient was considered in the analysis of before and after changes in physiological variables, including ICP and CPP, as well as the analysis of changes in laboratory values. The sample size for these analyses was therefore the number of eligible participants.

Pretreatment vital signs and laboratory measures in the analysis were those recorded closest in time prior to the administration of 23.4% NaCl. Posttreatment vital signs used in the analysis were recorded a minimum of 10 min following the completion of drug administration. Posttreatment laboratory measures were recorded a minimum of 60 min following drug administration. All laboratory measures used in the analysis were within 12 h of drug administration. Institutional practice requires that a serum sample for testing of electrolytes and renal function be obtained prior to initiation of any new osmotic agent, such as mannitol or an infusion of 3% NaCl, although clinicians are not required to obtain the results of such testing prior to administration of the new osmotic agent. The laboratory changes described herein are based on repeat testing performed following administration of 23.4% NaCl and prior to initiation of new osmotic agents and therefore reflect the use of 23.4% NaCl alone rather than multiple osmotic agents used together. Physiological changes also reflect values before and after use of 23.4% NaCl alone.

23.4% NaCl Institutional Protocol

Our institution's protocol restricts administration of 23.4% NaCl to patients with acutely elevated ICP or clinical concern for ongoing or threatened cerebral herniation. Approval of an attending neurointensivist, neurosurgeon, or trauma surgeon is required. Administration through central venous access is preferred but not required, particularly in the setting of cerebral herniation. The rationale for this provision is to avoid delays in treatment, in which the risk of death or devastating brain injury outweighs the risk of the more localized and reversible injury that may result from extravasation. Administration of each 30-ml (4 mEq/ml) dose is performed as an intravenous push over at least 10 min to minimize the risk of hypotension. In adults, the minimum dose used is one vial (30 ml = 120 mEq), and a second vial may be administered immediately afterward at the discretion of the provider on the basis of clinical response.

Statistical Analysis

Descriptive statistics were calculated by using proportions for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Associations between variables and outcomes of interest were tested by using the χ^2 or Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Only the first administration of 23.4% NaCl in each patient was used in all comparative analyses of administration via central and peripheral venous access, as well as the analysis of before and after change in physiological and laboratory variables, to avoid error from multiple administrations in the same patient. When two vials (60 ml) were administered, all before and after changes in physiological and laboratory variables were adjusted per vial (30 ml) by dividing the change value by 2. We therefore assumed a linear change in all physiological and laboratory variables following administration of 23.4% NaCl such that each vial achieved the same quantum of change for an individual patient at a given time. The threshold for statistical significance was a two-sided p value less than 0.05. Statistical analyses were performed by using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium).

Results

A total of 141 patients met eligibility criteria; 38 had an ICP monitor in place at the time of drug administration.

Baseline characteristics of patients are in Table 1. The median age was 57 years (IQR 38–69), 64 (45%) patients were female, and the two most common diagnoses were traumatic brain injury and intracerebral hemorrhage, with 33 patients (23%) each. There were 299 administrations of 23.4% NaCl during the study period in these 141 patients, of which 242 (80.9%) were through central venous access and 57 (19.1%) through peripheral venous access. Four patients received 23.4% NaCl via peripheral venous access twice, and one patient received 23.4% NaCl via peripheral access three times. As expected from the parameters of our institutional protocol, suspected cerebral herniation was significantly more frequent prior to administration via peripheral venous access ($p=0.003$), and a significantly smaller proportion of patients who received 23.4% NaCl via peripheral venous access had ICP monitoring in place at the time of administration ($p=0.01$).

Safety

Safety outcomes are in Table 2. Among 57 administrations via peripheral venous access, there was one recognized instance of extravasation during administration; this did not result in visible tissue injury. In another case, administration of the medication via peripheral venous access was terminated when the patient who was sufficiently awake to respond complained of pain at the injection site after a small volume was administered. There was no documented occurrence of thrombophlebitis, cellulitis, or tissue damage in either group. There were no instances of hemolysis or osmotic demyelination. Although several patients had varying degrees of pulmonary edema at the time of administration of the drug, medical records did not reflect worsening of pulmonary edema or oxygenation in any patient following administration of 23.4% NaCl. None of the patients who received 23.4% NaCl more than once via peripheral access suffered any complications.

A decrease in SBP of at least 20 mm Hg was noted following 33 of 299 (11%) administrations of 23.4% NaCl. Only 1 of 299 (0.3%) administrations was followed by a drop in MAP to 65 mm Hg or lower. No alternate cause of hypotension could be identified during this episode. Twenty-two of thirty-three (67%) instances of fall in SBP by at least 20 mm Hg were associated with potential alternate or exacerbating factors, such as rapid sequence

Table 1 Distribution of baseline variables

Variable	All patients ($N=141$)	23.4% NaCl administered via central venous catheter ($n=90$)	23.4% NaCl administered via peripheral intravenous access ($n=51$)	*p* value
Baseline variables				
Age, median (IQR) (yr)	57 (38–69)	56 (37–64)	60 (40–74)	0.10
Sex, female, *n* (%)	64 (45%)	39 (43%)	25 (49%)	0.60
Body mass index, median (IQR)	27 (23–33)	28 (24–33)	27 (23–32)	0.42
Diagnosis category, *n* (%)				0.08
Acute ischemic stroke	19 (13%)	15 (17%)	4 (8%)	–
Acute liver failure	7 (5%)	7 (8%)	0 (0%)	–
Cardiac arrest	6 (4%)	6 (7%)	0 (0%)	–
Intracerebral hemorrhage	33 (23%)	20 (22%)	13 (25%)	–
Infectious	4 (3%)	3 (3%)	1 (2%)	–
Posterior reversible encephalopathy syndrome	1 (< 1%)	1 (1%)	0 (%)	–
Subarachnoid hemorrhage	23 (16%)	12 (13%)	11 (22%)	–
Traumatic brain injury	33 (23%)	19 (21%)	14 (27%)	–
Tumor	15 (11%)	7 (8%)	8 (16%)	–
Clinical concern for cerebral herniation, *n* (%)	88 (62%)	47 (52%)	41 (80%)	0.003
ICP monitoring at time of administration, *n* (%)	38 (27%)	31 (34%)	7 (14%)	0.010
Dose administered, *n* (%)				0.38
30 ml	121 (86%)	79 (88%)	42 (82%)	–
60 ml	20 (14%)	11 (12%)	9 (18%)	–

ICP intracranial pressure, *IQR* interquartile range, *NaCl* sodium chloride

P values are for the univariate analysis

Table 2 Safety outcomes, efficacy for the reduction of ICP and augmentation of CPP, and impact on physiological and laboratory variables

Variable or outcome	All patients ($N=141$)	23.4% NaCl administered via central venous catheter ($n=90$)	23.4% NaCl administered via peripheral intravenous access ($n=51$)	*p* value
Safety outcomes, *n* (%)				
Extravasation	1 (0.7)	0 (0)	1 (2)	
Tissue injury or necrosis	0 (0)	0 (0)	0 (0)	
Pain during injection	1 (0)	0 (0)	1 (2)	
Pulmonary edema (new or worsening)	0 (0)	0 (0)	0 (0)	
Osmotic demyelination	0 (0)	0 (0)	0 (0)	
Death	70 (50)	39 (43)	31 (61)	0.08
Efficacy and change in physiological variables (per 30-ml vial)				
Δ MAP, median (IQR) (mm Hg)	−2 (−10 to +6)	−1 (−9 to +9)	−4 (−12 to +3)	0.04
SBP decrease by ≥ 20 mm Hg, *n* (%)	24 (17)	12 (13)	12 (24)	0.10
Δ HR, median (IQR) (beats per min)	0 (−4 to +6)	+1 (−2 to +7)	−3 (−8 to +4)	0.02
Δ ICP, median (IQR) (mm Hg)[a]	−14 (−23 to −5)[a]	−13 (−19 to −5)[a]	−24 (−27 to −11)[a]	0.21[a]
Δ CPP, median (IQR) (mm Hg)[a]	+16 (+8 to +21)[a]	+16 (+7 to +21)[a]	+15 (+9 to +21)[a]	0.87[a]
Change in laboratory values (per 30-ml vial)				
Δ sodium, median (IQR) (mEq/l)	+4 (+2 to +6)	+3.5 (+2 to +6)	+4 (+3 to +7)	0.09
Δ chloride, median (IQR) (mEq/l)	+5 (+3 to +8)	+4 (+2 to +7)	+6 (+5 to +9)	0.01
Δ potassium, median (IQR) (mEq/l)	0 (−0.25 to +0.25)	0 (−0.2 to +0.3)	−0.1 (−0.5 to +0.18)	0.04
Δ bicarbonate, median (IQR) (mmol/l)	−0.5 (−1 to +1)	−0.5 (−1 to +1)	0 (−2 to 1)	0.89
Δ creatinine, median (IQR) (mg/dl)	−0.02 (−0.07 to +0.04)	−0.02 (−0.07 to +0.03)	−0.02 (−0.10 to +0.04)	0.79
Δ hemoglobin, median (IQR) (g/dl)	−0.6 (−1.6 to −0.1)	−0.35 (−1.18 to 0)	−1.2 (−1.88 to −0.53)	0.007

CPP cerebral perfusion pressure, *HR* heart rate, *ICP* intracranial pressure, *IQR* interquartile range, *MAP* mean arterial pressure, *NaCl* sodium chloride, *SBP* systolic blood pressure, Δ, change in value from prior to administration of 23.4% NaCl

P values are for the univariate analysis

[a] Only includes the 38 patients (31 with central venous administration and 7 with peripheral venous administration) with ICP monitoring at the time of drug administration

intubation performed by using medications such as propofol; up-titration of infusions such as propofol, dexmedetomidine, and nicardipine; or recent administration of agents such nimodipine. Two of these episodes occurred in the setting of fever and clinical suspicion for sepsis.

Efficacy and Impact on Laboratory Values

Resolution of signs of herniation, such as pupillary asymmetry, were clearly documented in 19 of 88 (22%) patients who were treated with 23.4% NaCl for suspected cerebral herniation. Persisting signs of herniation were documented in 46 of 88 (52%) patients, and in 23 of 88 (26%) patients, documentation was insufficient to determine whether resolution had occurred. Resolution of signs of cerebral herniation was clearly observed in 9 of 47 (19%) herniating patients in whom administration was via central venous access, as opposed to 10 of 41 (24%) herniating patients in whom administration was via peripheral venous access ($p=0.61$).

The before and after magnitude of change in physiological and laboratory variables per 30 ml of 23.4% NaCl administered is in Table 2, and the analysis of statistical significance of the difference in values before and after 23.4% NaCl administration is in Table 3. Across all patients (Table 2), median (IQR) changes per 30-ml vial of 23.4% NaCl administered were as follows: ICP, −14 mm Hg (−23 to −5); CPP, +16 mm Hg (+8 to +21); sodium, +4 mEq/l (+2 to +6); chloride, +5 mEq/l (+3 to +8); and hemoglobin, −0.6 g/dl (−1.6 to −0.1). As expected, a statistically significant reduction in ICP ($p<0.0001$), along with a significant increase in CPP ($p=0.004$), sodium ($p<0.0001$), and chloride ($p<0.0001$), was observed across patients following administration of 23.4% NaCl (Table 3). No statistically significant changes in MAP, heart rate, potassium, bicarbonate, or creatinine were observed across all patients following administration (Table 3). Of note, a significant reduction in hemoglobin ($p=0.006$) was observed (Table 3).

The median fall in ICP (−13 mm Hg [central] vs. −24 mm Hg [peripheral], $p=0.21$) and median

Table 3 Change in physiological and laboratory variables following administration of 23.4% NaCl (per 30-ml vial)

Variable	Prior to administration of 23.4% NaCl	Following administration of 23.4% NaCl	*p* value
Physiological variables			
MAP, median (IQR) (mm Hg)	96 (83–108)	93 (85–103)	0.34
HR, median (IQR) (beats per min)	79 (67–95)	78 (67–96)	0.46
ICP, median (IQR) (mm Hg)	27 (23–40)	17 (11–20)	< 0.0001
CPP, median (IQR) (mmHg)	62 (51–74)	75 (64–86)	0.004
Laboratory variables			
Sodium, median (IQR) (mEq/l)	141 (138–144)	146 (142–151)	< 0.0001
Potassium, median (IQR) (mEq/l)	3.9 (3.6–4.2)	3.9 (3.7–4.3)	0.63
Chloride, median (IQR) (mEq/l)	108 (104–115)	114 (109–121)	< 0.0001
Bicarbonate, median (IQR) (mmol/l)	24 (22–26)	23 (21–25)	0.15
Creatinine, median (IQR) (mg/dl)	0.81 (0.63–1.12)	0.74 (0.61–1.14)	0.42
Hemoglobin, median (IQR) (g/dl)	11.4 (9.1–13.7)	10.3 (8.5–12.3)	0.006

Includes all 141 patients, except for the analysis of ICP and CPP, which only includes the 38 patients (31 with central venous administration and 7 with peripheral venous administration) with ICP monitoring at the time of drug administration. *P* values are for the univariate analysis

CPP cerebral perfusion pressure, *HR* heart rate, *ICP* intracranial pressure, *IQR* interquartile range, *MAP* mean arterial pressure, *NaCl* sodium chloride

increase in CPP (+16 mm Hg [central] vs. +15 mm Hg [peripheral], $p=0.87$) following peripheral administration was at least equal to that following central administration, as was the median rise in sodium (+3.5 mEq/l [central] vs. +4 mEq/l [peripheral], $p=0.09$). A significantly greater median fall in MAP (−1 mm Hg [central] vs. −4 mm Hg [peripheral], $p=0.04$), heart rate (+1 beat per minute [central] vs. −3 beats per minute [peripheral], $p=0.02$), potassium (0 mEq/l [central] vs. −0.1 mEq/l [peripheral], $p=0.04$), and hemoglobin (−0.35 g/dl [central] vs. −1.2 g/dl [peripheral], $p=0.007$) was seen following peripheral administration compared with central administration, along with a significantly higher rise in chloride (+4 mEq/l [central] vs. +6 mEq/l [peripheral], $p=0.01$), although no instances of hypotension or hemolysis were observed following administration via peripheral venous access, and the magnitude of these differences was quite small.

Discussion

Our study shows no difference in the occurrence of serious adverse effects following peripheral and central administration of 23.4% NaCl. There were no instances of thrombophlebitis, cellulitis, or tissue damage following 57 administrations of 23.4% NaCl via peripheral venous access. One patient reported pain during injection, which led to termination of the dose. Administration via peripheral venous access appeared to be equally efficacious for the reduction of ICP and augmentation of CPP compared with administration via central venous access. Overall, adverse events following administration of 23.4% NaCl were uncommon, with only one instance of hypotension, which occurred following central administration. Changes in physiological variables and laboratory values were likely confounded by patients' critical illness. Therefore, the minor differences between peripheral and central administration in reductions of MAP, heart rate, potassium, and hemoglobin almost certainly reflect the greater severity of neurological illness in patients who received 23.4% NaCl peripherally as well as confounding factors, such as concomitant rapid sequence intubation and fluid resuscitation. This was expected because our institutional protocol specifies that peripheral administration may be resorted to mostly in the setting of an emergency, such as cerebral herniation, whereas central venous access was available in the majority of patients who received the drug to treat an elevation in measured ICP but were otherwise stable. A significantly greater fall in MAP (median −1 mm Hg [central] vs. median −4 mm Hg [peripheral], $p=0.04$) and a greater percentage of patients with a 20-mm Hg fall in SBP (not statistically significant, 13% central vs. 24% peripheral, $p=0.10$) was seen with peripheral venous administration. However, there was no significant difference in augmentation of CPP (median +16 mm Hg [central] vs. median +15 mm Hg [peripheral], $p=0.87$), and the observed differences likely reflect confounding by indication and clinical status. Consistent with several other studies, our findings confirm the efficacy of 23.4% NaCl, regardless of route of administration, for reduction of ICP and augmentation of CPP (Table 3). We also did not find evidence of a consistent reduction in bicarbonate or rise in creatinine following administration, suggesting that the risk of hyperchloremic metabolic acidosis and acute kidney

injury is low following a bolus dose. One notable finding of our study was a statistically significant, if relatively small (median 0.6 g/l), fall in hemoglobin following administration of 23.4% NaCl. We had insufficient data to establish etiology, although minor hemolysis, hemodilution from concomitant fluid resuscitation, and blood loss from decompressive surgery are plausible explanations.

Although 23.4% NaCl has likely been administered via peripheral venous access at other institutions, our study is the first to systematically demonstrate that such administration is safe and effective. Peripheral venous administration permits expedient treatment of patients with herniation syndromes in a variety of settings, obviating the time and expertise required to obtain central venous or intraosseous access, as well as the risks of such access. Concerns about safety currently limit the use of 23.4% NaCl vials, otherwise convenient for transportation and storage, by military medics in tactical evacuation and prolonged field care. The ability to use this agent through peripheral venous access will also facilitate the management of neurological emergencies in the emergency department, by rapid response teams in the inpatient setting, and in civilian prehospital settings. Our findings suggest that in adult patients, the risks of administration via peripheral venous access appear to be minimal. However, central venous access should likely be obtained in critically ill patients who require ongoing administration of hypertonic saline. This is analogous to the administration of vasopressors via peripheral venous access for limited periods of time for the treatment of shock until central access is available [19].

Several studies have shown that 3% NaCl can be infused via peripheral venous access, with a low rate of complications [17, 20, 21]. Although 23.4% NaCl has much higher osmolarity (8008 mOsm/l) than 3% NaCl (1026 mOsm/l), it is administered as discrete bolus doses over 10 min in the context of emergencies. The time period of risk of extravasation-related injury is therefore much lower compared with that for continuous infusion of 3% NaCl over hours or days. In a study of 66 patients, the majority of whom (64%) were treated for hyponatremia alone, the median duration of infusion of 3% NaCl via peripheral venous access was 14 h, and the rate of serious adverse events was 6%, with no permanent injuries [17]. In this study, all but one patient received the infusion in their upper limbs, and 60% of peripheral intravenous cannulas were 20 gauges or smaller. In another study of 213 neurocritical care patients treated with 3% NaCl via peripheral venous access alone for a median duration of about 45 h, an infusion-related reaction occurred in 15 (7%) patients [20]. In this series, most patients received the infusion at an antecubital site (64%) and had an 18-gauge (47%) or 20-gauge (47%) cannula.

The main limitation of our study is its retrospective observational nature and relatively small sample size. Ninety patients received their first dose of 23.4% NaCl via central venous access and 51 via peripheral venous access. It is possible that mild tissue injury or thrombophlebitis occurred following administration but was not documented in the medical record. This is unlikely; however, evaluation and documentation of skin and device-related (including intravenous cannulas) injury has been a focus of nursing quality assurance at our institution during the study period. Also, the risk of mild tissue injury or thrombophlebitis likely does not outweigh the benefit of expeditious treatment of a life-threatening condition. We were unable to systematically assess pain during administration, except for one documented instance, because most patients were poorly responsive as a result of brain injury or sedation. The administration of other medications that commonly cause pain during peripheral administration, such as 50% dextrose and propofol, is considered appropriate for the treatment of serious medical conditions. Although studies that have examined the safety of 3% NaCl infusions administered via peripheral venous access have described the site and gauge of peripheral venous access [17, 20], this information was not available in our registry. We were therefore unable to establish the comparative safety of administration through smaller versus larger veins and cannulas. However, our protocol did not restrict use via peripheral venous access by site or size, and we did not observe any serious complications with peripheral administration. We assumed a linear relationship between dose and response to quantify the impact of each 30-ml vial on physiological and laboratory parameters when 60 ml was administered as a single dose. This assumption may not be valid under all circumstances. Laboratory measures of hemolysis were not routinely checked. Less severe or subclinical hemolysis might have been overlooked, a distinct possibility given the small but significant drop in hemoglobin levels seen following administration. However, clinically relevant hemolysis was not observed. Finally, our analysis of the ability of 23.4% NaCl to reverse cerebral herniation was limited by the available documentation and the difficulty in separating the impact of 23.4% NaCl from the impact of other measures implemented immediately following administration, such as craniotomy and decompression. However, other studies have established the efficacy of 23.4% NaCl for the reversal of herniation [4].

Conclusions

Peripheral venous administration of 23.4% NaCl is safe and achieves a reduction in ICP equivalent to administration via central venous access.

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Author contributions
LF made substantial contributions to design, acquisition of data, and analysis and interpretation of data and drafting the article. DH made substantial contributions to design, acquisition of data and critical revision for important intellectual content. SCR made substantial contributions to design and critical revision for important intellectual content. OK made substantial contributions to design and critical revision for important intellectual content. Craig A. Williamson Osama made substantial contributions to design and critical revision for important intellectual content. VR made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data and to drafting the article.

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References

1. Cook AM, Morgan Jones G, Hawryluk GWJ, Mailloux P, McLaughlin D, Papangelou A, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care. 2020;32(3):647–66.
2. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury. Fourth Ed Neurosurg. 2014;80(1):6–15.
3. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(4):1222–38.
4. Koenig MA, Bryan M, Lewin JL 3rd, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70(13):1023–9.
5. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. Stroke. 2002;33(1):136–40.
6. Ware ML, Nemani VM, Meeker M, Lee C, Morabito DJ, Manley GT. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. Neurosurgery. 2005;57(4):727–36 (**Discussion 727–36**).
7. Suarez JI, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, et al. Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med. 1998;26(6):1118–22.
8. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quickel RR. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. Neurosurgery. 2009;65(6):1035–41 (**Discussion 1041–32**).
9. Alnemari AM, Krafcik BM, Mansour TR, Gaudin D. A comparison of pharmacologic therapeutic agents used for the reduction of intracranial pressure after traumatic brain injury. World Neurosurg. 2017;106:509–28.
10. Mangat HS, Chiu YL, Gerber LM, Alimi M, Ghajar J, Hartl R. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. J Neurosurg. 2015;122(1):202–10.
11. Dorman HR, Sondheimer JH, Cadnapaphornchai P. Mannitol-induced acute renal failure. Medicine (Baltimore). 1990;69(3):153–9.
12. Palma L, Bruni G, Fiaschi AI, Mariottini A. Passage of mannitol into the brain around gliomas: a potential cause of rebound phenomenon. A study on 21 patients. J Neurosurg Sci. 2006;50(3):63–6.
13. Al-Benna S, O'Boyle C, Holley J. Extravasation injuries in adults. ISRN Dermatol. 2013;2013:856541.
14 Wang J, Fang Y, Ramesh S, Zakaria A, Putman MT, Dinescu D, et al. Intraosseous administration of 23.4% NaCl for treatment of intracranial hypertension. Neurocrit Care. 2019;30(2):364–71.
15. Knight J, Rayi A. Transtentorial herniation. [Updated 2021 Feb 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560536/
16. Dornhofer P, Kellar JZ. Intraosseous vascular access. [Updated 2020 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554373/
17. Dillon RC, Merchan C, Altshuler D, Papadopoulos J. Incidence of adverse events during peripheral administration of sodium chloride 3. J Intensive Care Med. 2018;33(1):48–53.
18. Perez CA, Figueroa SA. Complication rates of 3% hypertonic saline infusion through peripheral intravenous access. J Neurosci Nurs. 2017;49(3):191–5.
19. Pancaro C, Shah N, Pasma W, Saager L, Cassidy R, van Klei W, et al. Risk of major complications after perioperative norepinephrine infusion through peripheral intravenous lines in a multicenter study. Anesth Analg. 2020;131(4):1060–5.
20. Jones GM, Bode L, Riha H, Erdman MJ. Safety of continuous peripheral infusion of 3% sodium chloride solution in neurocritical care patients. Am J Crit Care. 2016;26(1):37–42.
21. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. JAMA Intern Med. 2021;181(1):81–92.