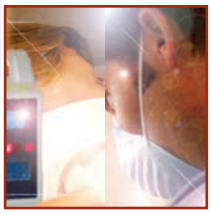

Safety of Continuous Peripheral Infusion of 3% Sodium Chloride Solution in Neurocritical Care Patients

By G. Morgan Jones, PharmD, BCPS, BCCCP, Lauren Bode, PharmD, Heidi Riha, PharmD, and Michael J. Erdman, PharmD, BCPS

Background Numerous drug information resources recommend that continuous intravenous 3% sodium chloride solution be administered via a central catheter.
Objectives To evaluate the incidence of infusion-related reactions and electrolyte abnormalities in neurocritical care patients treated with continuous intravenous infusion of 3% sodium chloride solution via a peripheral catheter.
Methods Data on patients treated with continuous intravenous infusion of 3% sodium chloride solution at 2 academic medical centers were evaluated retrospectively to determine the administration site. Electronic notes on catheter status were reviewed to determine the occurrence of infusion-related reactions. Prespecified thresholds were used to assess electrolyte abnormalities.
Results Of 213 patients who had peripheral continuous intravenous infusions of 3% sodium chloride solution, 15 (7%) had infusion-related reactions. Administration was changed to a central catheter in 56 patients (26.3%), but only 5 changes were due to an infusion-related reaction. Most (157 patients, 73.7%) received their entire treatment peripherally, for a median duration of 44 hours, 3 minutes. The most common electrolyte abnormalities were hyperchloremia in 49.3% and hypokalemia in 46.9% of patients.
Conclusion Current recommendations that a central catheter is required for continuous intravenous infusion of 3% sodium chloride solution should be reevaluated. Only a few patients who had peripheral infusions had infusion-related reactions. Electrolyte abnormalities occurred frequently with peripheral infusion, but the clinical importance of the abnormalities remains unclear.
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Various concentrations of hypertonic saline are effective in reducing intracranial pressure and cerebral edema associated with numerous neurological injuries.[1-3] One treatment with hypertonic saline often used is a continuous intravenous infusion of 3% sodium chloride solution.[4] However, few studies have evaluated the safety of this treatment in neurocritical care patients.[4] Complications such as hypernatremia, hyperchloremic acidosis, and hypokalemia have been reported.[4-6]

In addition, no data are available on the proper site for administration of a continuous intravenous infusion of 3% sodium chloride solution in adults. Tertiary references suggest administration via a large-bore central catheter, although this recommendation is not based on actual safety evaluations in adult patients.[7] Peripheral intravenous administration of 3% sodium chloride solution has been studied in children, and results of a few studies[8,9] have indicated limited safety concerns. Proposed safety concerns associated with peripheral administration of a continuous intravenous infusion of 3% sodium chloride solution include extravasation, phlebitis, tissue ischemia, and venous thrombosis.[7,10-12] Despite these proposed concerns, no studies have been done on the expected incidence of adverse effects when the continuous infusion is given peripherally.

Patients could have a central catheter placed solely for the continuous intravenous infusion of 3% sodium chloride solution.

On the basis of available drug references and the theoretical safety concerns, patients may have a central catheter placed solely for the continuous intravenous infusion of 3% sodium chloride solution. In the multicenter, retrospective, cohort study described here, our aim was to determine the incidence of infusion-related reactions requiring intervention in patients who received continuous intravenous infusions of 3% sodium chloride solution via a peripheral catheter.

About the Authors

G. Morgan Jones is a clinical pharmacy specialist, Methodist University Hospital, and an assistant professor of clinical pharmacy, neurology, and neurosurgery, University of Tennessee Health Sciences Center, Memphis, Tennessee. **Lauren Bode** is a postgraduate year 1 pharmacy resident, University of North Carolina Hospitals and Clinics, Chapel Hill, North Carolina. **Heidi Riha** is a postgraduate year 2 pharmacy resident, Methodist University Hospital. **Michael J. Erdman** is a clinical pharmacist, University of Florida Health, Jacksonville, Florida.

Corresponding author: G. Morgan Jones, PharmD, BCPS, BCCCP, Assistant Professor, Clinical Pharmacy, Neurology, and Neurosurgery, University of Tennessee Health Sciences Center, 1265 Union Ave, Memphis, TN 38104 (e-mail: morgan.jones@mlh.org).

Methods

We conducted a retrospective, multicenter cohort study of all patients who had continuous intravenous infusion of 3% sodium chloride solution via a peripheral catheter and were discharged from 1 of the 2 included institutions between September 15, 2011, and September 14, 2014. Approval of the study was obtained from the institutional review boards at both sites before data collection began, and all work was carried out according to the ethical standards set forth in the Helsinki Declaration of 1975. The 2 medical centers are large, urban, teaching hospitals with dedicated neurocritical care teams. Both institutions allow peripheral administration of continuous intravenous infusion of 3% sodium chloride solution; the maximum infusion rate is 75 mL/h at one hospital and 30 mL/h at the other hospital.

At both institutions, daily documentation of all intravenous sites is required and any change or complications associated with an intravenous site must be noted by the bedside nurse, allowing ready assessment of infusion-related reactions. One hospital requires documentation of the score on the visual infusion phlebitis scale[13]; as a standard practice, a peripheral catheter is removed if the score is greater than 1. Data on all patients who had continuous intravenous infusion of 3% sodium chloride solution were evaluated to determine if the infusion was administered via a peripheral catheter at any point during the hospitalization, because both institutions require that the site of administration be included in the charting of continuous intravenous infusions of 3% sodium chloride solution. We excluded data on patients who were less than 18 years old or more than 89 years old, pregnant, or currently lactating. We also excluded data on patients with a history of end-stage renal disease, syndrome of inappropriate antidiuretic hormone, or diabetes insipidus because of the inability to accurately assess electrolyte abnormalities in these patients that might have been associated with continuous intravenous infusion of 3% sodium chloride solution.

The primary outcome was the occurrence of any infusion-related reaction requiring intervention. We collected information on the site of administration that included needle gauge, intravenous location, any change in administration site, various administration rates (initial, maximum, and weighted mean), and the duration of infusion. Information on infusion-related reactions was obtained from required documentation in the electronic medical record and from supplemental physician documentation if clarification was needed.

The secondary objective was to assess the incidence of electrolyte abnormalities associated with continuous intravenous infusion of 3% sodium chloride solution. Although we did not expect any difference associated with the site of the infusion, limited data are available on the exact incidence of these abnormalities in patients receiving continuous intravenous infusions of 3% sodium chloride solution. All recorded measurements of electrolytes obtained during continuous intravenous infusion of 3% sodium chloride solution were assessed and were classified as abnormal if they met the following definitions: hypokalemia (serum level of potassium < 3.5 mEq/L), hyperchloremia (serum level of chloride > 110 mEq/L), hypernatremia (serum level of sodium > 155 mEq/L), and hypobicarbonatemia (serum level of bicarbonate < 20 mEq/L). We recorded whether an abnormality occurred and the total number of episodes. Other information collected to characterize the patient sample included age, height, weight, sex, race or ethnicity, type of neurological injury, requirement for mechanical ventilation, hospital and intensive care unit lengths of stay, and in-hospital mortality. The lowest score on the Glasgow Coma Scale documented within 24 hours of continuous intravenous infusion of 3% sodium chloride solution was also recorded to classify the severity of neurological injuries. Medical history of chronic kidney disease not requiring hemodialysis and chronic heart failure were also collected because of the potential of these conditions to affect secondary outcomes.

Results

A total of 213 neurocritical care patients received peripheral continuous intravenous infusion of 3% sodium chloride solution. Most of the patients were African American males admitted with intracerebral hemorrhage (37.1%) or acute ischemic stroke (36.2%). Only a few patients had chronic kidney disease (2.3%) or chronic heart failure (7.5%). A total of 105 patients (49.3%) required mechanical ventilation, and 53 patients (24.9%) died during their admission. Of those patients who survived, the median duration of hospitalization was 11.3 days, with 6.1 days spent in the neurocritical care unit (Table 1).

Table 1
Characteristics of 213 patients in the study

Characteristic	Result
Male, No. (%) of patients	127 (59.6)
African American, No. (%) of patients	114 (53.5)
Age, median (IQR), y	59 (51-71)
Height, median (IQR), cm	172.7 (165.1-180.0)
Weight, median (IQR), kg	80.7 (67.8-97.5)
Score on Glasgow Coma Scale at admission, median (25%-75% interquartile range)	10 (6-13)
Neurological injury, No. (%) of patients	
Acute ischemic stroke	77 (36.2)
Intracerebral hemorrhage	79 (37.1)
Traumatic brain injury	16 (7.5)
Other	41 (19.2)
Length of stay, median (IQR), d	
Hospital	11.3 (6.1-18.4)
Intensive care unit	6.1 (3.3-12)
Medical history, No. (%) of patients	
Chronic kidney disease	5 (2.3)
Chronic heart failure	16 (7.5)

Abbreviation: IQR, interquartile range.

Median duration of treatment with continuous intravenous infusion of 3% sodium chloride solution (hours:minutes) for the whole population regardless of change in infusion site was 51:07 (interquartile range [IQR], 26:32-81:54). Peripheral intravenous sites were exclusively used for administration in 157 patients (73.7%), for a median duration of 44:43 (IQR, 21:15-74:48). The site of administration was changed to a central catheter in 56 patients (26.3%) after a median duration of 19:32 (IQR, 7:11-37:54; Table 2). If a central catheter is placed, common practice at both institutions is to administer continuous intravenous infusions of 3% sodium chloride solution via the central catheter. Most patients had an 18-gauge (47.4%) or a 20-gauge (46.5%) needle used for catheter placement at an antecubital site (64.3%). The primary outcome, infusion-related reaction, occurred in only 15 patients (7%); phlebitis 9 times and extravasation 6 times. No documented episodes of thrombophlebitis occurred. Table 3 is a detailed description of all 15 events and treatments. Of note, 8 of the 15 patients who experienced an infusion-related reaction had continuous

The primary observation was for the occurrence of any infusion-related reaction requiring intervention.

Table 2
Information on infusion of 3% sodium chloride solution in 213 patients

Characteristic	Result
Infusion rate, median (IQR), mL/h	
Initial	30 (20-30)
Maximum	30 (25-40)
Weighted mean[a]	30 (24.4-34.7)
Peripheral administration site, No. (%) of patients	
Antecubital	137 (64.3)
Forearm	36 (16.9)
Hand	22 (10.3)
Wrist	18 (8.5)
Peripheral administration site needle gauge, No. (%) of patients	
16	8 (3.8)
18	101 (47.4)
20	99 (46.5)
22	5 (2.3)
Initial peripheral catheter switched to central administration, No. (%) of patients	56 (26.3)
Duration of infusion, median (IQR), h:min	
Total (n = 213)	51:07 (26:32-81:54)
Peripheral site only (n = 157)	44:43 (21:15-74:48)
Peripheral site before switch to central site (n = 56)	19:32 (7:11-37:54)

Abbreviation: IQR, interquartile range.

[a] Calculated by assessing the duration of treatment at each infusion rate used, then dividing the mean of the total volume received by the duration of treatment.

intravenous infusion of 3% sodium chloride solution resumed at an alternative peripheral intravenous site with no further documented reactions. Only 5 patients had the site of administration changed to a central catheter because an infusion-related reaction occurred. Furthermore, 8 events occurred in a catheter with a 20-gauge needle and 7 in catheters with an 18-gauge needle. Last, the rate of infusion varied across all infusion reactions. Only 3 events occurred at rates greater than 50 mL/h; most of the majority of events (10) occurred at rates of 30 mL/hr or less.

The most commonly occurring electrolyte abnormalities were hyperchloremia in 105 patients (49.3%) and hypokalemia in 100 patients (46.9%) (Table 4). Baseline serum level of sodium among all patients was 139 mEq/L (IQR, 135-142 mEq/L), with values peaking at 149 mEq/L (IQR, 142-155 mEq/L) during treatment. Median serum osmolarity was 290 mOsm/L (IQR, 278-298 mOsm/L) at baseline; the peak level was 308 mOsm/L (IQR, 291-319 mOsm/L).

Discussion

Because of current recommendations included in various drug information resources, patients may have a central catheter placed solely for the purpose

Table 3
Infusion-related reactions requiring documentation and intervention (n = 15)

Event	Infusion rate, mL/h	Needle gauge	Infusion site	Reaction type	Intervention
1	20	20	Antecubital	Extravasation	Changed to alternative peripheral catheter; no further reactions documented
2	40	18	Forearm	Phlebitis	Changed to central catheter
3	20	18	Wrist	Phlebitis	Changed to central catheter
4	20	20	Antecubital	Extravasation	Changed to alternative peripheral catheter; no further reactions documented
5	35	18	Hand	Phlebitis	Changed to central catheter
6	30	20	Antecubital	Phlebitis	Changed to alternative peripheral catheter; no further reactions documented
7	15	20	Hand	Phlebitis	Changed to alternative peripheral catheter; no further reactions documented
8	15	20	Forearm	Extravasation	Changed to alternative peripheral catheter; no further reactions documented
9	75	18	Antecubital	Extravasation	Infusion stopped completely
10	30	18	Wrist	Phlebitis	Changed to central catheter
11	30	18	Antecubital	Phlebitis	Changed to central catheter
12	75	20	Antecubital	Phlebitis	Changed to alternative peripheral catheter; no further reactions documented
13	50	20	Antecubital	Extravasation	Changed to alternative peripheral catheter; no further reactions documented
14	25	18	Antecubital	Phlebitis	Changed to alternative peripheral catheter; no further reactions documented
15	20	20	Hand	Extravasation	Infusion stopped completely

of administering continuous intravenous infusions of 3% sodium chloride solution. Our study is the first on the safety of peripheral administration of 3% sodium chloride solution in adults. We observed a limited number of infusion-related reactions even when 3% sodium chloride solution was administered peripherally as a continuous infusion for a prolonged duration. We also determined various sites of administration, needle gauges, and infusion rates that might aid in characterizing the safety of continuous intravenous infusion of 3% sodium chloride solution via a peripheral catheter.

Commonly, the maximum osmolarity of peripherally infused solutions is limited to 900 mOsm/L to avoid infusion-related reactions such as extravasation, thrombophlebitis, and tissue necrosis. This threshold most likely is extrapolated from published evaluations of peripheral administration of various osmolar loads of total parenteral nutrition formulas. Few clinical data are available on solutions outside of those related to parenteral nutrition.[14] Because a 3% solution of sodium chloride solution has an osmolarity of 1026 mOsm/L, numerous tertiary references[7,10-12] recommend that the solution be infused through a central catheter to avoid infusion-related reactions. Administration via a central catheter is preferred, but peripheral administration is acceptable in critically ill patients when immediate therapy is needed.[12] In the United States alone, more than 5 million central catheters are placed, accounting for 15 million days of treatment with central access.[15,16] Although these catheters are valuable tools in patient care, they are associated with numerous complications that may worsen mortality and increase associated health care costs.[17-19] Research has indicated that catheter-associated complications, ranging from infection and symptomatic thrombosis to pneumothorax,[15] can occur with up to 15% to 20% of catheters, depending on the site of placement.[20] The Centers for Disease Control and Prevention estimates that the mean additional cost for 1 central catheter–associated bloodstream infection is $16 550, indicating the marked impact these complications can have on health care costs.[21] Because few infusion-related reactions occurred in our study even when infusion rates were high as 75 mL/h, we think that using literature on peripheral administration of formula for total parenteral nutrition to determine recommendations for peripheral administration of 3% sodium chloride solution may not be appropriate and that current tertiary references should be reevaluated. Safe administration of continuous intravenous infusions of 3% sodium chloride solution via a peripheral catheter may help avoid unnecessary placement of central catheters, facilitating a reduction in associated complications and unnecessary health care costs.

Table 4
Electrolyte abnormalities in 213 patients

Abnormality	Value
Hypokalemia (potassium <3.5 mEq/L)	
No. (%) of patients	100 (46.9)
No. of episodes, median (IQR)	2 (1-2)
Hyperchloremia (chloride >110 mEq/L)	
No. (%) of patients	105 (49.3)
No. of episodes, median (IQR)	2 (1-4)
Hypernatremia (sodium >155 mEq/L)	
No. (%) of patients	47 (22.1)
No. of episodes, median (IQR)	1 (1-4)
Hypobicarbonatemia (bicarbonate <20 mEq/L)	
No. (%) of patients	19 (8.9)
No. of episodes, median (IQR)	1 (1-2)

Abbreviation: IQR, interquartile range.

Although no previous studies have been done on peripheral administration of 3% sodium chloride solution in adults, the results of several studies support the safety of peripheral administration in children.[8,9] In a retrospective cross-sectional study, Brenkert et al[8] investigated administration of a bolus of 3% sodium chloride solution in 56 pediatric patients at an urban children's hospital, with 87% of doses administered via a peripheral catheter. No patient had indications of phlebitis or local tissue destruction. Bolus doses given in as short a time as 3 minutes were well tolerated, without apparent adverse effects. In a second retrospective study, Luu et al[9] evaluated 101 children who received a 3% sodium chloride solution during the course of critical care transport, primarily as a bolus dose infused over wide duration of time (4-180 minutes). A peripheral catheter was used in 95% of patients, and no infusion reactions occurred.

Additionally, evidence is limited on the incidence of electrolyte disturbances associated with continuous intravenous infusion of 3% sodium chloride solution. In our study, the most common electrolyte disturbance was hyperchloremia, which occurred in 49.3% of patients. However, a much smaller percentage (16.9%) of the patients in whom hyperchloremia developed actually had an intervention initiated to treat this disturbance. Hypokalemia requiring intervention was also common (46.9% overall, 43.6% requiring intervention). Hypernatremia, however, occurred much less frequently (22.1%). In a previous study[22] in patients with cerebrovascular diseases, the overall incidence of severe electrolyte imbalances was low; only 5 patients had severe hypokalemia (serum potassium level <3 mmol/L). Overall, 21% of patients in the study[22] experienced

a sodium level greater than 159 mmol/L, although no adverse sequelae occurred. Hauer et al[22] did not report information on hyperchloremia associated with continuous intravenous infusion of 3% sodium chloride solution. The definitions used in the study[22] were less stringent than the definitions we used, a characteristic that may explain the difference in rates between their study and our study. However, because of the large amount of sodium and chloride administered with prolonged continuous intravenous infusion of 3% sodium chloride solution, further research on the clinical implication of marked electrolyte abnormalities is needed.

Our study has several limitations. First, our retrospective design was reliant on accurate nurses' documentation of assessment of the primary outcome. Additionally, we cannot provide information on the clinical importance of electrolyte abnormalities. Our study also has several notable strengths. It was conducted at 2 centers with dedicated neurocritical care units. Both medical centers also have documentation policies in place on changes to the sites of intravenous catheters that help increase the likelihood of accurate documentation of all infusion-related events. Finally, both institutions commonly administer 3% sodium chloride solutions as prolonged continuous infusions, providing valuable data on the safety of this intervention when used for longer durations.

Conclusions

Few infusion-related reactions occurred among patients treated with continuous intravenous infusion of 3% sodium chloride solution via a peripheral catheter, even at rates as high as 75 mL/h. Current recommendations suggesting that a central catheter is required for administration of continuous intravenous infusions of 3% sodium chloride solution should be reevaluated, and providers should consider a peripheral site when the sole reason for placement of a central catheter is infusion of 3% sodium chloride solution. Electrolyte abnormalities occurred frequently, but the clinical importance of the abnormalities remains unclear. Further research is needed to elucidate the impact of the electrolyte disturbances on clinical outcomes.

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FINANCIAL DISCLOSURES
None reported.

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