

Complication Rates of 3% Hypertonic Saline Infusion Through Peripheral Intravenous Access

Claudia Andira Perez, Stephen A. Figueroa

ABSTRACT

Introduction: Hyperosmolar therapy with hypertonic saline (HTS) is a cornerstone in the management of intracranial hypertension and hyponatremia in the neurological intensive care unit. Theoretical safety concerns remain for infiltration, thrombophlebitis, tissue ischemia, and venous thrombosis associated with continuous 3% HTS administered via peripheral intravenous (pIV) catheters. It is common practice at many institutions to allow only central venous catheter infusion of 3% HTS. **Methods:** Hospital policy was changed to allow the administration of 3% HTS via 16- to 20-gauge pIVs to a maximum infusion rate of 50 mL/h in patients without central venous access. We prospectively monitored patients who received peripheral 3% HTS as part of a quality improvement project. We documented gauge, location, maximum infusion rate, and total hours of administration. Patients were assessed for infiltration, erythema, swelling, phlebitis, thrombosis, and line infection. **Results:** There were 28 subjects across 34 peripheral lines monitored. Overall, subjects received 3% HTS for a duration between 1 and 124 hours with infusion rates of 30 to 50 mL/h. The rate of complications observed was 10.7% among all subjects. Documented complications included infiltration (n = 2), with an incidence of 6%, and thrombophlebitis (n = 1), with an incidence of 3%. **Conclusions:** There has been a long concern among healthcare providers, including nursing staff, in regard to pIV administration of prolonged 3% HTS infusion therapy. Our study indicates that peripheral administration of 3% HTS carries a low risk of minor, nonlimb, or life-threatening complications. Although central venous infusion may reduce the risk of these minor complications, it may increase the risk of more serious complications such as large vessel thrombosis, bloodstream infection, pneumothorax, and arterial injury. The concern regarding the risks of pIV administration of 3% HTS may be overstated and unfounded.

Keywords: intracranial hemorrhage, neurocritical care, neuropharmacology, safety, subarachnoid hemorrhage

Management of hyponatremia in the setting of increased intracranial pressure (ICP) and neuroendocrine abnormalities, such as cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion, remain key management issues in the neurologic intensive care unit (ICU).

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The efficacy of hypertonic saline (HTS) in reducing ICP has been shown in multiple animal and human studies in various conditions such as traumatic brain injury, subarachnoid hemorrhage, acute ischemic stroke, brain tumors, and acute hepatic failure. Hypertonic saline has been shown to improve cerebral perfusion pressure by decreasing ICP and increasing mean arterial pressure.^{1,2} When compared with mannitol, HTS seems to be more effective in reducing ICP and has the added benefit of intravascular volume expansion. This is beneficial in conditions such as subarachnoid hemorrhage where hypovolemia is associated with poor outcomes.³⁻⁵ Hypertonic saline can be administered in a bolus or infusion, and mode of administration is dependent on time needed for efficacy. In acute neurological deterioration, with elevations in ICP and concern for herniation, bolus administration is most effective. Infusion therapy may benefit in reducing ICP burden and maintaining a more stable cerebral perfusion pressure. Continuous infusion of HTS can lead to decreased frequency of ICP crisis and decreased mortality.^{1,6}

Cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion can lead to an acute symptomatic hyponatremia. In this setting, rapid correction to reverse clinical symptoms (seizures,

obtundation) can be best accomplished by continuous HTS infusion at higher rates. Once normonatremia is achieved, maintenance of a therapeutic or prophylactic hypernatremia (145–155 mEq/L) is essential, especially in the setting of cerebral edema and increased ICP. Slower infusion can allow for simultaneous control of sodium and volume balance, which can allow for a more gradual change in sodium concentration. Although the literature supports the use of continuous intravenous HTS as effective in the management of increased ICP, hyponatremia, and acute resuscitation, there are many theoretical concerns with regard to safety in the administration of these therapies via peripheral venous catheters.

Studies looking at the administration of HTS in models of hemorrhagic shock showed equal effectiveness in resuscitation with both peripheral and central infusions of 7.5% NaCl/6% dextran 70.⁷ Histological examination of the veins and arteries injected showed no significant difference in abnormalities other than mild inflammatory responses at the sites of catheter passage.^{7,8} Additional clinical studies have not shown local site complications with infusion of 3% to 7.5% of HTS with infusion for 7 days; these have been further supported with gross inspection and histological examination.^{7,9–11} Despite these data, concerns regarding the peripheral infusion of HTS continue to be raised based on extrapolated data from studies published about total parenteral nutrition. These studies showed that prolonged hyperosmolar solution infusion through peripheral lines had a significant time- and concentration-dependent relationship with thrombophlebitis and other complications. Specifically, Timmer and Schipper¹² noted that the osmolarity rate tended to correlate with phlebitis rate, which was defined as rate = mOsm/L (osmolarity of solution) $\times$ L/h (infusion rate). The independent evaluation of osmolarity of the solution and volume infused correlated poorly with phlebitis rate. The limitation in using these data is that the infusate used was different in composition than an infusion of only HTS. Experimental animal studies have shown that tolerability of hyperosmolarity may be related to the duration of infusion in regards to the development of phlebitis and not directly related to osmolarity of the solution itself.¹³ Concern regarding peripheral thrombosis and thrombophlebitis is not supported with human data.¹⁴

There has been a concern with the infusion of HTS causing hemolysis, given studies that showed that HTS administration in dogs induced hemolysis. The study used 25%, 15%, and 7.5% NaCl infusions and compared central versus peripheral administration of the 25% and 15% solutions. Severe hemolysis was reported with peripheral injection of 25% and

Peripheral administration of 3% hypertonic saline carries low risk of complications.

15% solutions as compared with mild hemolysis with central administration. There was no hemolysis with 7.5% solution, which was only administered peripherally.⁸ There was no macroscopic or microscopic alteration in the cephalic (peripheral) veins, which were used for infusion. In vitro, it was noted that a 900-mosm/L concentration with HTS saline was needed to induce hemolysis in human and dog red blood cells; this serum osmolarity was not achieved with any of the in vivo administration. There was no hemolysis detected in the 300- to 600-mosm/L range. Studies looking specifically at the administration of 7.5% HTS/6% dextran-70 solution in human red blood cells in vitro have not shown significant hemolysis.¹⁵

There are little published safety data of specifically prolonged administration of HTS through peripheral venous catheters. Safe administration in critically ill patients of 3% and 7.5% NaCl/dextran has been used for hypovolemic resuscitation in adults and children without increased rates of phlebitis, despite large volume infusion of hypertonic fluids.^{10,16} Many studies looking at HTS administration have not found increased rates of line infection and thrombotic events (deep venous thrombosis [DVT], pulmonary embolism, or dural venous thrombosis) in general.¹⁷ Central venous catheters allow for greater tolerance of more acidic and hyperosmolar infusion but are associated with complications such as pneumothorax, sepsis, and DVT. They require placement by an experienced physician and require aseptic catheter care to prevent catheter-related bloodstream infections.¹⁸

There have been little clinical data gathered, although clinically practiced infusion of peripheral 3% HTS saline is often accepted and occurs without any significant observed complications. In our study, we sought to prospectively gather data on patients who received HTS in our surgical ICU to assess the complication rates we saw in our neurological patient population.

Methods

The study is a quality review project to assess safety in clinical practice. Hospital policy had changed to allow the administration of 3% HTS in approved areas via 16- to 20-gauge peripheral intravenous (pIV) catheters up to a maximum infusion rate of 50 mL/h in patients without central venous access. We prospectively

collected data of patients admitted to Parkland Hospital Surgical ICU who were treated with 3% HTS through a pIV catheter. There was a retrospective chart review conducted before analysis to account for any missing variables. All known patients who were initiated on 3% HTS through a peripheral line were included in the study; there were no exclusion criteria.

Demographic data were gathered on patients and indication for hyperosmolar therapy. There was paper and electronic chart documentation, which allowed nursing staff to document the site of pIV catheter, gauge of catheter, and maximum infusion rate. While the patient received hyperosmolar therapy, routine assessment by nurses and physicians was made to detect any complications. Patients were assessed for infiltration, erythema, swelling, phlebitis, thrombosis, and signs of line infection. There was a protocol to discontinue 3% HTS via peripheral administration if central venous access was obtained for another indication other than HTS therapy or if dose needed exceeded the protocol (50 mL/h). At the completion of hypertonic therapy, total hours were compiled for the duration of use of the pIV catheter. Line assessment was continued 24 hours after peripheral administration was discontinued. The date, time, and reason for the discontinuation of catheter were documented in the electronic chart.

Infusion therapy was routinely initiated at 30 mL/h and titrated up to no greater than 50 mL/h for extended periods of therapy. If patients were noted to require higher doses of HTS, bolus was given, and central access was obtained to allow for higher dosing.

We calculated the incidence rate of complication for the number of patients who received peripheral administration of HTS.

Results

Data were collected from October 2013 to May 2014. Total enrolled subjects were 28, and 34 peripheral lines were monitored; demographic information is in Table 1. Infusion rates across the subjects were between 30 and 50 mL/h. Total infusion duration of infusion was 1 to 124 hours, with a mean duration of 36 hours. Treatment data are available in Table 2.

The rate of complications observed in general was 10.7% ($n = 3$) among all subjects and 11.7% ($n = 4$) per line assessed in the 3 patients with complications. Documented complications included infiltration ($n = 2$), with an incidence in this study of 6%. There were no major complications that occurred with local infiltration of the IV except for thrombophlebitis ($n = 1$), with an incidence of approximately 3%. Our data were compared with historical controls; we reviewed the

TABLE 1. Patient Demographic

Patients	N = 28
Age, y	14-79
	39 ± 19
Sex	Male, 19; female, 9
Type of injury	SAH: 4 (14%)
	TBI: 11 (39%)
	ICH: 5 (18%)
	SDH: 3 (11%)
	Mass: 3 (11%)
	Abscess: 1 (3%)
	AIS: 1 (3%)

Note. AIS = acute ischemic stroke; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage; TBI = traumatic brain injury.

literature for incidence of complications from peripheral vein infusion such as infiltration, extravasation, and thrombophlebitis.

There was 1 incidence of right brachial vein thrombosis in 1 patient who received 3% HTS via pIV for 1 hour. For this patient, HTS infusion was delivered to the left hand for 31 hours with noted infiltration. Infusion was switched to the right arm, and he developed infiltration at site. Bilateral upper extremity Dopplers were performed, and right brachial and basilic vein thrombus was present; the left was patent and free of thrombus.

Discussion

Thrombophlebitis (pain, erythema, swelling, and palpable thrombosis at a canalized vein) is one of the most common complications of peripheral IV insertion. In general, rates of local complications of peripheral vein infusion such as thrombophlebitis are approximately 25% to 35%.^{19,20} Many factors increase the risk for thrombophlebitis, such as the duration of catheterization, catheter material, type of infusion, and catheter site infection. The duration of catheterization has been the most important predictor of peripheral vein infusion-related phlebitis.²⁰ Infiltration or extravasation of intravenous solution into the subcutaneous tissue can lead to tissue ischemia and skin necrosis, with incidence rates as high as 16% to 78%.²¹⁻²³ Risk factors for infiltration or extravasation are prolonged IV therapy of greater than 5 days, previous infiltration, catheter readjustment, use of infusion pump, and intermittent administration of infusates.²¹ There has been a long concern among healthcare providers, including nursing staff, in regard to pIV administration of prolonged 3% HTS infusion therapy. Our study

TABLE 2. Treatment Data

Catheters	N = 34
Duration, h	1–124, 36 ± 30
Rate infusion, mL/h	30–50, 39 ± 10
Gauge catheter	16–20
Anatomic placement	Arm: 23 (68%)
	Hand: 6 (18%)
	Foot: 4 (12%)
	Ankle: 1(3%)

indicates that peripheral administration of 3% HTS carries a low risk of minor, nonlimb, or life-threatening complications. Our data showed that there was much lower incidence of complications than was reported in the literature, with infiltration/extravasation in approximately 6% and thrombophlebitis in 3% of the subjects. We did not observe complications such as tissue ischemia, tissue necrosis, or increased incidence of line infection in our study. There was 1 reported case of DVT in our study that does not seem to be related to prolonged administration of hyperosmolar infusion.

The lower incidence of complications that we observed may be related to the line care provided. These peripheral lines were to be used exclusively for HTS and were not subject to frequent changes as seen with other lines. There may have been a bias in providing better line care with more frequent checks. There may have been a decreased incidence of mechanical manipulation given the decreased number of infusates given per line. Studies have shown that appropriate line selection and care given by specialized teams can decrease the incidence of thrombophlebitis and extravasation.²⁴

Central venous catheters and peripherally inserted central catheter lines have significant mechanical, infectious, and thrombotic complications associated with placement and use.²⁵ Major complications seen are catheter-related large vein thrombosis, central line–associated bloodstream infections, and insertion-related complications, such as pneumothorax and arterial puncture. Pulmonary emboli are seen in up to 15% of symptomatic peripherally inserted central catheter–related large vein thrombosis.²⁶ Pneumothorax is a reported complication in approximately 1.5% to 2.3% of subclavian catheterization, and thrombosis is a reported complication in 6.6% to 25% of femoral catheterizations.²⁷ Catheter-related bloodstream infections are a major complication of central venous access, with femoral catheterizations having the largest rate of complications.^{27,28} Severe complications with central venous catheters have led clinicians to reassess the safety profile of peripheral venous catheters in

administering previously restricted medication, such as vasoactive agents. In their study, Cardenas-Garcia et al²⁹ found that the administration of norepinephrine, dopamine, and phenylephrine by pIV access was feasible and safe.

The nature of our patient population in the neurological ICU warrants frequent use of hyperosmolar therapies for various neurological and medical conditions. It is important to elucidate the safety concerns that surround the peripheral administration of HTS therapy because this may decrease unnecessary central venous catheter placement, which has significant associated morbidity. This small prospective study was aimed at providing some answers to a frequently asked question in the ICU, in regard to safety of therapy, because there have not been published data before. We recognize the limitation of these data in that we have a small sample size, use of historical controls as a comparison group, and lack of control intersubject and intrasubject patient data on lines used. We, however, believe that these novel safety data of specific complications from peripheral vein infusion of 3% HTS at rates of up to 50 mL/h will provide a basis by which further studies will be built on. We hope that this can help guide safe nursing administration of 3% HTS because, in our experience, we did not have a high incidence of complications when compared with historical controls. This practice may help elucidate the value of high quality of care of peripheral lines as a nursing initiative to minimize minor complications and help reduce unnecessary central line placement, central line days, and hospital-acquired infections.

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