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Predictors of Acute Kidney Injury in Neurocritical Care Patients Receiving Continuous Hypertonic Saline

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Abstract

Background and Purpose: Continuous intravenous 3% hypertonic saline (HTS) infusions are commonly used for the management of cerebral edema following severe neurologic injuries. Despite widespread use, data regarding the incidence and predictors of nephrotoxicity are lacking. The purpose of this study was to describe the incidence and identify predictors of acute kidney injury (AKI) in neurocritical care patients administered continuous infusion HTS. **Methods:** This was an institutional review board–approved, multicenter, retrospective cohort study of patients receiving HTS infusions at 2 academic medical centers. A univariate analysis and multivariable logistic regression were used to identify predictors of AKI. Data regarding AKI were evaluated during treatment with HTS and up to 24 hours after discontinuation. **Results:** A total of 329 patients were included in our analysis, with 54 (16%) developing AKI. Those who developed AKI experienced significantly longer stays in the intensive care unit (14.8 vs 11.5 days; $P = .006$) and higher mortality (48.1% vs 21.9%; $P < .001$). We identified past medical history of chronic kidney disease (odds ratio [OR]: 9.7, 95% confidence interval [CI]: 1.9-50.6; $P = .007$), serum sodium greater than 155 mmol/L (OR: 4.1, 95% CI: 2.1-8.0; $P < .001$), concomitant administration of piperacillin/tazobactam (OR: 3.9, 95% CI: 1.7-9.3; $P = .002$), male gender (OR: 3.2, 95% CI: 1.5-6.6; $P = .002$), and African American race (OR: 2.6, 95% CI: 1.3-5.2; $P = .007$) as independent predictors of AKI. **Conclusion:** Acute kidney injury is relatively common in patients receiving continuous HTS and may significantly impact clinical outcomes.

Keywords
hypertonic saline, acute kidney injury, cerebral edema

Introduction

Cerebral edema is a common complication associated with a variety of neurologic injuries. Damage to the cellular membrane may cause imbalances in intracellular sodium and water concentrations, leading to refractory intracranial hypertension and herniation. Sodium chloride 3%, also referred to as hypertonic saline (HTS), has become a mainstay in the treatment of cerebral edema due to its rapid onset of vasoconstriction and reduced cerebrovascular volume, thus reducing intracranial hypertension.[1,2] Administration of HTS as a continuous infusion was first described in 1998. However, the limited number of publications on its use hinders the ability to determine an accurate incidence of adverse effects.[3] Currently, pulmonary edema, diabetes insipidus, hyperchloremia, and acute kidney injury (AKI) are the most widely reported adverse effects associated with the use of HTS.[4,5]

Understanding the incidence of AKI with HTS is vital, as AKI has been shown to progress to long-term hemodialysis and negatively affect morbidity.[6,7] Identification of patients vulnerable to AKI may also help prescribers better evaluate risks versus benefits for HTS administration. The purpose of this study was to describe the incidence and identify predictors of AKI in neurocritical care patients administered continuous infusion HTS.

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Methods

Patient Characteristics and Study Variables

This was a retrospective cohort study conducted at 2 academic medical centers, each with dedicated neurocritical care teams. This study was approved by institutional review boards at both the University of Tennessee Health Sciences Center and the University of Florida. A waiver of informed consent was granted.

Neurocritical care patients who received HTS were identified through electronic medical records. Standard practice at both institutions is to administer HTS as a continuous infusion to maintain induced hypernatremia. Other hyperosmolar therapy, including mannitol or 23.4% sodium chloride boluses, may also have been utilized for acute intracranial hypertension. Inclusion criteria included the following—patients aged 18 to 89 years, admission dates between 2012 and 2014, and cerebral edema that necessitated continuous HTS infusions. Exclusion criteria included the following—pregnant or lactating patients, past medical history of diabetes insipidus or syndrome of inappropriate antidiuretic hormone, prehospital end-stage renal disease requiring dialysis, baseline serum sodium >155 mmol/L, and inconsistent documentation of laboratory results during HTS treatment.

Patient characteristics collected included demographics, admission Glasgow coma scale (GCS), primary neurological diagnosis, history of chronic kidney disease (CKD) and chronic heart failure, and baseline and peak serum sodium and serum osmolality. We also assessed concomitant administration of medications associated with nephrotoxicity, including diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), piperacillin/tazobactam, vancomycin, sulfamethoxazole/trimethoprim, penicillins, acyclovir, fluoroquinolones (specifically ciprofloxacin and levofloxacin), aminoglycosides, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, contrast media, mannitol, and 23.4% sodium chloride boluses.[8-10] Hypertonic saline infusion parameters collected included initial, maximum, and weighted mean infusion rate as well as duration of treatment. Acute kidney injury was determined using the Acute Kidney Injury Network (AKIN) criteria and was assessed during HTS infusion and for up to 48 hours after discontinuation.[11] Stage 1 AKI was defined as an increase in serum creatinine of more than or equal to 0.3 mg/dL) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline. Stage 2 AKI was defined as an increase in serum creatinine to more than 200% to 300% (>2- to 3-fold) from baseline, and stage 3 AKI was defined as an increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL with an acute increase of at least 0.5 mg/dL).

Statistical Analysis

Continuous parametric data were presented as mean $\pm$ standard deviation and analyzed using Student *t* test. Continuous nonparametric data were analyzed using Mann-Whitney test and presented as median (25%-75% interquartile range). Nominal data were analyzed using either χ^2 test or Fisher exact test. After a univariate analysis comparing patients with and without AKI was performed, multivariable logistic regression was conducted to determine independent risk factors for AKI. Covariates with $P < .2$ from the univariate analysis were entered into a stepwise, multivariable logistical regression model. Two-tailed statistical tests were utilized, and a $P < .05$ was determined to represent statistical significance. Results are reported as adjusted odds ratio with corresponding 95% confidence intervals (CIs). All data were analyzed using SPSS software (IBM Corp Released 2012; IBM SPSS Statistics for Windows, version 21.0, Armonk, New York).

Results

A total of 337 patients were included, with intracerebral hemorrhage (34.4%), ischemic stroke (33.5%), and traumatic brain injury (11.0%) being the most common neurological diagnoses. Overall, the median GCS was 8 (6-13) and 57.9% of included patients required mechanical ventilation. The median intensive care unit (ICU) length of stay was 7.5 (4.0-14.2), whereas a median of 12 (7-23) days were spent in the hospital overall. Of the 75.7% of patients who survived their admission, 67.5% were discharged to a facility, such as a rehabilitation hospital or skilled nursing facility, and 32.5% were discharged home. Patients received HTS for a median time of (hours: minutes) 49:04 (25:45-82:12), with 325 (96.4%) patients receiving HTS for more than 12 hours. The primary outcome of AKI occurred in 54 (16.4%) patients, with 28 (8.3%) classified as AKIN stage 1 and the remaining 26 patients evenly split between AKIN stages 2 and 3. Only 3 (0.9%) patients required hemodialysis secondary to AKI. Median time from initiation of HTS infusion to occurrence of AKI was 79:30 [31:23-105:24]. Patients with AKI had significantly longer lengths of stay in the ICU (10.9 vs 7.1 days; $P = .006$) and the hospital (14.8 vs 11.5 days; $P = .05$) and experienced higher in-hospital mortality (48.1% vs 21.9%; $P < .001$; Table 1).

Patients who developed AKI were more likely to be male (75.9% vs 55.8%; $P = .006$), African American (70.4% vs 51.2%; $P = .01$), and have a history of CKD (7.4% vs 1.1%; $P = .003$; Table 2). Baseline serum sodium and baseline serum osmolality were similar between AKI and non-AKI groups. Hyperchloremia, severe hypernatremia (serum sodium > 155 mmol/L), and hyperosmolality were more common in the AKI group (Table 2).

Patients who developed AKI were also more likely to receive a loop diuretic (84.6% vs 65.6%; $P = .07$), NSAID (20.4% vs 10.9%; $P = .06$), hypotonic intravenous fluids (13.0% vs 2.8%; $P = .004$), piperacillin/tazobactam (24.1% vs 7.4%; $P < .001$), and mannitol (29.6% vs 14.8%; $P = .008$; Table 3). No other differences were observed between groups in relation to the receipt of other nephrotoxic medications.

Table 1. Hypertonic Saline Administration Information and Discharge Characteristics.[a]

	Non-AKI Group (n = 283)	AKI Group (n = 54)	*P*
Administration rate, mL/h			
Initial	30 (25-30)	28 (20-30)	.62
Initial range	10-75	10-60	–
Maximum	30 (25-45)	28 (20-45)	.79
Maximum range	10-75	10-100	–
Average	30 (22-34.1)	28.6 (20-36.5)	.83
Average range	10-75	10-60	–
Duration of infusion (hh: mm)	47:42 (23:55-83:59)	56:20 (34:25-80:20)	.46
Length of stay, days			
Hospital	11.5 (7-21.1)	14.8 (9.5-27.0)	.05
Intensive care unit	7.1 (3.9-13.3)	10.9 (5.5-20.5)	.006
Discharge status, n (%)			
Expired	62 (21.9)	26 (48.1)	<.001
Facility[b]	143 (64.7)	25 (89.3)	.009
Home[b]	78 (35.3)	3 (10.7)	.009

Abbreviation: AKI, acute kidney injury.
[a]All data are presented as median (25%-75% interquartile range) unless otherwise noted.
[b]Analyzed used only those who survived admission (non-AKI = 221; AKI = 28).

Multivariable logistic regression analysis identified past medical history of CKD, male gender, African American race, treatment with piperacillin/tazobactam, and severe hypernatremia as independent factors associated with AKI (Table 4). The logistic regression was adequately calibrated based on a nonsignificant Hosmer-Lemeshow goodness-of-fit P value = .87, and the model had good discrimination based on the area under the receiver–operator characteristic curve of 0.77 (95% CI: 0.71-0.84). Past medical history of CKD was a very strong predictor, as it associated with an almost 10-fold increase in the incidence of AKI, with male gender and African American race being associated with a 4-fold increase in AKI. Modifiable risk factors such as severe hypernatremia and treatment with piperacillin/tazobactam were both associated with a 4-fold increase in the incidence of AKI. No variables were associated with a decreased incidence of AKI. All other variables with a $P < .2$ from the univariate analysis were not significantly associated with AKI in the multivariable model.

Discussion

Acute kidney injury has been shown to occur in up to half of all ICU patients.[7] It has been shown to occur in 14% of patients with ischemic stroke and 21% of those with

Table 2. Patient Characteristics.[a]

	Non-AKI Group, n = 283	AKI Group, n = 54	*P*
Male, n (%)	158 (55.8)	41 (75.9)	.006
African American race, n (%)	145 (51.2)	38 (70.4)	.01
Age, years[b]	58.8 ± 16.0	55.5 ± 14.4	.13
Height, cm[b]	172 ± 9.9	175.5 ± 11	.03
Weight, kg	79.8 (66.1-95.3)	86.1 (70-107)	.01
Admission Glasgow coma scale score	9 (6-13)	8 (6-11)	.18
Mechanical ventilation, n (%)	153 (54.1)	42 (77.8)	.001
Neurologic injury, n (%)			
Acute ischemic stroke	94 (33.2)	19 (35.2)	.78
Intracerebral hemorrhage	97 (34.3)	19 (35.2)	.90
Traumatic brain injury	30 (10.6)	7 (13.0)	.61
Other	62 (21.9)	9 (16.7)	.39
Past medical history, n (%)			
Chronic kidney disease	3 (1.1)	4 (7.4)	.003
Chronic heart failure	23 (8.1)	8 (14.8)	.12
Serum sodium, mg/dL			
Baseline	139 (135-142)	140 (136-142)	.16
Peak	148 (142-154)	155 (149-158)	<.001
Serum osmolality, mOsm/L			
Baseline	289 (277-297)	292 (282-302)	.12
Peak	304 (291-317)	322 (308-328)	<.001
Electrolyte abnormalities			
Chloride > 110 mmol/L	151 (55.1)	43 (79.6)	<.001
Sodium > 155 mmol/L	52 (19)	25 (46.3)	<.001
Osmolality > 320 mOsm/L	51 (18.9)	28 (51.9)	<.001

Abbreviation: AKI, acute kidney injury.
[a]All data are presented as median (25%-75% interquartile range) unless otherwise noted.
[b]Data are presented as mean ± standard deviation.

Table 3. Concomitantly Administered Treatments.[a]

	Non-AKI Group (n = 283)	AKI Group (n = 54)	P
Angiotensin-converting enzyme inhibitors	94 (33.2)	23 (42.6)	.19
Angiotensin receptor blockers	8 (2.8)	3 (5.6)	.30
Antimicrobials			
Acyclovir	3 (1.1)	0 (0)	.45
Ampicillin/penicillin	11 (3.9)	3 (5.6)	.57
Ciprofloxacin/levofloxacin	20 (7.1)	7 (13.0)	.14
Gentamicin	6 (2.1)	1 (1.9)	.90
Piperacillin/tazobactam	21 (7.4)	13 (24.1)	<.001
Sulfamethoxazole/trimethoprim	7 (2.5)	2 (3.7)	.61
Vancomycin	75 (26.5)	20 (37.0)	.12
Contrast media	94 (33.3)	23 (42.6)	.19
Diuretics			
Loop	40 (65.6)	22 (84.6)	.07
Thiazide	26 (42.6)	6 (23.1)	.08
Nonsteroidal anti-inflammatory agents	30 (10.9)	11 (20.4)	.06
Hyperosmolar therapy			
Mannitol	42 (14.8)	16 (29.6)	.008
23.4% sodium chloride	3 (1.1)	1 (1.9)	.51
Additional IV fluids			
Isotonic	168 (59.4)	38 (70.4)	.13
Hypotonic	8 (2.8)	7 (13.0)	.004

Abbreviations: AKI, acute kidney injury; IV, intravenous.
[a]All data are presented as n (%).

Table 4. Multivariable Logistic Regression Analysis for Predictors of Acute Kidney Injury While Receiving Continuous Hypertonic Saline Infusion.

Variable	Odds Ratio	95% Confidence Interval	P
History of chronic kidney disease[a]	9.7	1.9-50.6	.007
Serum sodium >155 mmol/L	4.1	2.1-8.0	<.001
Treatment with piperacillin/tazobactam	3.9	1.7-9.3	.002
Male gender	3.2	1.5-6.6	.002
African American race	2.6	1.3-5.2	.007

[a]Not requiring hemodialysis prior to admission; Hosmer and Lemeshow goodness-of-fit test = 0.87; Receiver–operator characteristic area under the curve = 0.77 (95% confidence interval: 0.71-0.84); All other variables with $P < .2$ in univariate analysis did not predict outcome.

hemorrhagic stroke and is associated with longer length of stay and increased mortality,[7,12] making identification of patients at increased risk of AKI imperative. Our study is the first to evaluate AKI in a large population of neurocritical care patients and provide clinicians with factors that should be considered when initiating continuous HTS infusions. Correlating with the existing literature, patients in our study who developed AKI were found to have a significantly higher rate of all-cause mortality as well as extended hospital and ICU lengths of stay.[7,12] These data highlight the need for research that identifies factors that may be associated with AKI in patients started on HTS. Our study identified 5 predictors of AKI associated with HTS in patients with neurological injuries (1) history of CKD, (2) severe hypernatremia, (3) piperacillin/tazobactam, (4) male gender, and (5) African American race. As other nonmodifiable risk factors that were identified including African American race and male gender have been previously described,[13,14] we will focus our discussion on modifiable predictors.

Past medical history of CKD was the strongest predictor of AKI in our analysis. The relationship between preexisting kidney disease and AKI has been well documented in non-ICU populations.[15,16] Decreased nephron density, glomerular hypertrophy, and fibrosis lead to a decreased ability to concentrate urine and respond to nephrotoxic threats such as hypotension and medications.[17-19] Previous studies in ICU patients have only identified age of 75 years or older, nephrotoxic medications, sepsis, and history of hypertension as risk factors for AKI.[16] This is the first analysis to identify CKD as a risk factor for AKI in neurocritical care patients receiving HTS.

Although the exact mechanism of AKI secondary to HTS is not fully understood, severe hypernatremia due to HTS has been associated with AKI.[20] In 1 study, AKI was found in 9.0% of 736 consecutive patients presenting with subarachnoid hemorrhage (SAH).[21] The only significant risk factor for AKI was cumulative maximum serum sodium (hazard ratio = 1.06, 95% CI = 1.01-1.10; $P = .008$), which was used as a surrogate for HTS use. The authors used the AKIN criteria to determine AKI but did not report proportions of patients that received HTS. More patients in our study experienced AKI using the same criteria, though the severity of AKI was similar with most patients experiencing AKIN stage 1. Our study demonstrates a strong association between severe hypernatremia and AKI. Because the kidney has a limited ability to concentrate urine, it is possible that superfluous sodium excretion causes decreased excretion of other solutes and waste products.[22] Another retrospective analysis of prolonged HTS use in patients with traumatic brain injury, SAH, or ischemic stroke found that patients who experienced severe hypernatremia were at an increased risk for elevated blood urea nitrogen and serum creatinine.[5] The authors acknowledged that their use of arbitrary cutoffs for laboratory values and lack of an AKI stratification scale preclude comparison of their results to other studies. Our application of the AKIN criteria showed that most cases of AKI that developed were transient and did not progress to long-term hemodialysis.

Neurocritical care patients often have multiple risk factors for infection along with systemic inflammatory responses that could be attributable to sepsis or their neurologic injury.[23,24] Although early appropriate antimicrobial therapy has been associated with decreased ICU and hospital lengths of stay, antibiotics have the potential for significant adverse effects.[25] Treatment with vancomycin and piperacillin/tazobactam has been shown to increase the risk of AKI when compared to

the use of cefepime and vancomycin (odds ratio: 5.67, 95% CI: 1.66-19.33) in a mixed inpatient population.[9] Piperacillin alone has also been associated with competitive inhibition of renal tubular secretion, though the effect appears to reverse rapidly upon discontinuation.[8,26] We examined the association between each antibiotic and AKI separately, and piperacillin/tazobactam was the only agent associated with AKI in both the univariate and multivariable analysis. A common practice at both institutions was to empirically initiate both gram-positive and gram-negative coverage for possible hospital-acquired infections. Our study is the first to identify piperacillin/tazobactam usage in neurocritical care patients receiving HTS as a risk factor for AKI, with those receiving this agent being 290% more likely to develop AKI. Based upon our analysis, providers should consider less nephrotoxic options, such as cephalosporins, in neurocritical care patient concomitantly receiving continuous HTS if their local antibiogram permits.

Multiple interventions that are commonly thought to increase the incidence of AKI were not identified as significant risk factors in our analysis, including administration of mannitol, diuretics, contrast media, and other antimicrobials. Infrequent administration of aminoglycosides may have prevented them from being significant contributors, as only 2.1% of the overall cohort received these agents. Administration of contrast media was relatively common, with 34.7% of all patients receiving some type of iodinated contrast. Literature describing the incidence of contrast-induced AKI or nephropathy in patients with acute ischemic stroke estimates a 2% incidence of AKI, whereas a decrease in serum creatinine can be seen in roughly 1% of patients.[27-30] The absence of an association between these interventions and AKI may be due to selection bias or insufficient exposure within the study cohort. Further study is needed to definitively determine if they are as harmful in this population as they are in others.

Our study has several limitations outside of its retrospective design. Because we defined severe hypernatremia as a categorical variable, we can make no inferences as to the relationship between the risk of AKI and increases in serum sodium. Both institutions widely use HTS proactively in patients with a high risk of cerebral edema, which precluded the ability to have a comparator group with an equivalent severity of illness that did not receive HTS. We also did not examine whether the existence of multiple risk factors in a single patient have an additive effect on their risk for AKI. Other biomarkers for renal failure are not commonly collected at either institution.

However, our study also has several strengths, including its multicenter design and inclusion of a relatively large number of patients. The AKIN criteria are a well-described scale that has been validated in multiple ICU populations and allows for easy comparison between different populations.[11] Since patients must have received HTS, most patients had relatively severe neurologic injuries. Other clinicians who use HTS for nonneurologic indications may benefit from the risk factors we described as well. Our study is the largest analysis to date of risk factors associated with AKI in neurocritical care patients, and it identified several previously not described in this patient population. We identified 2 potentially modifiable risk factors that can be mitigated to decrease the incidence of AKI. Although severe hypernatremia is a common adverse effect associated with HTS, providers have little guidance with regard to the safe maximum serum sodium levels. Although previous literature has identified hypernatremia as a risk factor for AKI in patients with SAH, this is the first study to confirm that this risk factor exists across a wide range of neurologic injuries.[21] This is also the first study to identify piperacillin/tazobactam as a risk factor for AKI in neurocritical care.

Conclusion

Acute kidney injury occurred in 16% of patients receiving HTS for severe neurologic injuries in our study. Independent risk factors for the development of AKI included a history of CKD, serum sodium > 155 mmol/L, treatment with piperacillin/tazobactam, male gender, and African American race. Our study is the first to identify multiple risk factors for AKI specifically in neurocritical care and may give providers insight into how to decrease its incidence in patients with severe neurologic injuries receiving HTS. Clinicians should carefully monitor patients to avoid severe hypernatremia and limit the use of piperacillin/tazobactam concurrently with continuous HTS when possible.

Declaration of Conflicting Interests

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