Association of Hyponatremia and Clinical Prognosis in Neuro Critically Ill Patients

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Objective

To investigate the impact of hyponatremia severity on in-hospital mortality of neurocritically ill patients.

Methods

This was a retrospective, observational study of patients who were admitted at a tertiary university hospital, Seoul, Republic of Korea, neurosurgical intensive care unit (ICU) from January 2013 to December 2019. We included neurocritically ill patients whose serum sodium concentrations were obtained during the ICU admission. The primary endpoint was in-hospital mortality.

Results

A total of 903 patients were included in the final analysis. Hyponatremia was detected in 359 (39.8%) patients. There was no significant difference in in-hospital mortality between the no hyponatremia group and the hyponatremia group (8.8% vs. 9.7%, $p = 0.724$). However, the length of ICU stay was longer in the hyponatremia group than no hyponatremia group (282.3 ± 295.9 hr vs. 141.8 ± 89.3 hr, $p < 0.001$). In the multivariable analysis, severe hyponatremia (adjusted odds ratio [OR]: 5.41, 95% confidence interval [CI]: 1.23 – 20.54), malignancy (adjusted OR: 3.45, 95% CI: 1.29 – 9.72), continuous renal replacement therapy (adjusted OR: 6.15, 95% CI: 1.65 – 23.38), invasive intracranial pressure monitoring (adjusted OR: 0.39, 95% CI: 0.17 – 0.83) and Glasgow Coma Scale on ICU admission (adjusted OR: 0.6, 95% CI: 0.52 – 0.69) were significantly associated with in-hospital mortality.

Conclusion

Based on our findings, mild to moderate hyponatremia were not associated with clinical outcomes. However, severe hyponatremia was significantly associated with in-hospital mortality. Therefore, adequate and timely regulation of serum sodium level is important for favorable prognosis and survival of neurocritically ill patients.

Keywords: Hyponatremia; Prognosis; Neurosurgery; Intensive care unit

INTRODUCTION

Hyponatremia is a common electrolyte abnormality in hospitalized patients^{6,9,13,17}. It could be mild with nausea and vomiting or severe with lethargy, seizures, and loss of consciousness¹⁴. In the critically ill, especially neurocritically ill patients, hyponatremia is also a common electrolyte disorder and is associated with clinical prognosis^{13,14}. Hyponatremia may induce neurological complications including cerebral edema, increased intracranial pressure (ICP), seizures, altered mentality, and brain death due to exacerbation of brain edema⁶. In addition, neurocritically ill patients may be more vulnerable to hyponatremia and may develop clinical symptoms in the absence of severe hyponatremia^{6,16}. Therefore, inadequate or delayed hyponatremia treatment may lead to significant morbidity and mortality¹³ in neurocritically ill patients. However, the number of studies that have reported the correlation between hyponatremia severity and the clinical outcomes of neurocritically ill patients is limited. In this study, we aimed to evaluate the impact of hyponatremia severity on in-hospital mortality of neurocritically ill patients.

MATERIALS AND METHODS

Study population and design

This was a retrospective, single-center, observational study of patients who were admitted at the Samsung Medical Center, Seoul, Republic of Korea, neurosurgical intensive care unit (ICU) from January 2013 to December 2019. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB approval number: SMC 2020-09-082). Patients' records were reviewed and analyzed according to the Declaration of Helsinki. The requirement of informed consent was waived by the IRB due to its

retrospective nature. We included neurocritically ill patients and those who were on neurosurgical postoperative management, including brain tumor, subarachnoid hemorrhage, cerebral vascular surgery, intracerebral hemorrhage, cerebral infarction, traumatic brain injury, infection of the central nervous system. In addition, the patients should have been hospitalized in the ICU for more than 3 days or died within 3 days after ICU admission, and their serum sodium concentrations should have been obtained during the ICU admission. We excluded patients whose hypernatremia was above 145 mEq/L during their ICU stay, who had insufficient medical records, who had a 'do not resuscitation' order, who were admitted to departments other than neurosurgery, and who were transferred to other hospitals or with unknown prognosis (Fig. 1).

Definitions and outcomes In this study, the baseline characteristics such as comorbidities, behavioral risk factors, ICU management, and laboratory data were collected retrospectively using Clinical Data Warehouse. Our center constructed a "Clinical Data Warehouse Darwin-C" designed for investigators to search and retrieve de-identified medical records from electronic archives. The serum sodium levels were obtained at least once every day from all neurosurgical patients. Hyponatremia was defined as serum sodium < 135 mmol/L⁵. In addition, to help determine the association between the clinical outcomes and severity of hyponatremia, the patients were categorized into four subgroups: no hyponatremia (≥ 135 mEq/L), mild hyponatremia (130 – 134 mEq/L), moderate hyponatremia (125 – 129 mEq/L), and severe hypernatremia (< 125 mEq/L)⁵. In this study, the primary endpoint was in-hospital mortality.

Statistical analyses

All data are presented as mean $\pm$ standard deviation for contin-

Fig. 1. Study flow chart. ICU: Intensive care unit.

uous variables or frequencies and proportions for categorical variables. Data were compared using Student's *t*-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. A stepwise multiple logistic regression was performed to obtain a statistically meaningful predictor of in-hospital mortality. All tests were two-sided and *p* values of less than 0.05 were considered statistically significant. All statistical analyses were performed with R Statistical Software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 12,743 patients were admitted to the neurosurgical

ICU during the study period, among them 903 patients were included in the final analysis. The mean age of all the patients was 44.9 ± 24.4 years and 54.0% of patients were male. Hyponatremia was detected in 359 (39.8%) patients. Malignancy (66.0%) and hypertension (37.1%) were the most common comorbidities, while brain tumors (52.2%) and intracerebral hemorrhage (12.7%) were the most common reasons for ICU admission (Table 1).

Clinical outcomes of the overall study population

There was no significant difference in in-hospital mortality between the no hyponatremia group and the hyponatremia group (8.8% vs. 9.7%, *p* = 0.724). However, the length of ICU stay was longer in the hyponatremia group than no hyponatremia group (282.3 ± 295.9 hr vs. 141.8 ± 89.3 hr, *p* < 0.001). In addition,

Table 1. Baseline characteristics

Variable	Normal (n = 544)	Hyponatremia (n = 359)	<i>p</i> value
Patient demographics			
Age (year)	43.4 ± 24.1	47.2 ± 24.7	0.021
Sex, male	276 (50.7)	212 (59.1)	0.017
Comorbidities			
Malignancy	332 (61.0)	264 (73.5)	<0.001
Hypertension	147 (27.0)	112 (31.2)	0.200
Diabetes mellitus	44 (8.1)	41 (11.4)	0.118
Chronic kidney disease	19 (3.5)	31 (8.6)	0.002
Cardiovascular disease	19 (3.5)	13 (3.6)	0.999
Chronic liver disease	13 (2.4)	12 (3.3)	0.518
Behavioral risk factors			
Current alcohol consumption	100 (18.4)	68 (18.9)	0.901
Current smoking	55 (10.1)	38 (10.6)	0.906
Cause of ICU admission			0.017
Brain tumor	276 (50.7)	195 (54.3)	
Intracerebral hemorrhage	69 (12.7)	46 (12.8)	
Vascular surgery	70 (12.9)	34 (9.5)	
Traumatic brain injury	54 (9.9)	35 (9.7)	
Subarachnoid hemorrhage	52 (9.6)	34 (9.5)	
Central nervous system infection	8 (1.5)	14 (3.9)	
Cerebral infarction	15 (2.8)	1 (0.3)	
APACHE II score on ICU admission	5.0 ± 5.0	5.9 ± 5.5	0.006
Glasgow Coma Scale on ICU admission	13.1 ± 2.4	13.0 ± 2.3	0.696
ICU management			
Mechanical ventilation	182 (33.5)	162 (45.1)	0.001
Continuous renal replacement therapy	10 (1.8)	12 (3.3)	0.225
Invasive ICP monitoring	206 (37.9)	177 (49.3)	0.001
Use of mannitol [*]	268 (49.3)	140 (39.0)	0.003
Use of glycerin [*]	141 (25.9)	96 (26.7)	0.843
Use of vasopressors	36 (6.6)	26 (7.2)	0.819

Data are presented as numbers (%) or means $\pm$ standard deviations.

APACHE: Acute Physiology and Chronic Health Evaluation, ICP: intracranial pressure, ICU: intensive care unit, ICP: intracranial pressure.

^{*}Some patients received more than one hyperosmolar agent.

there were no significant differences in the clinical outcome according to the hyponatremia severity-based groups except hospital length of stay ($p < 0.001$) (Table 2).

In the multivariable analysis, severe hyponatremia (adjusted odds ratio [OR]: 5.41, 95% confidence interval [CI]: 1.23 – 20.54), malignancy (adjusted OR: 3.45, 95% CI: 1.29 – 9.72), continuous renal replacement therapy (adjusted OR: 6.15, 95% CI: 1.65 – 23.38), invasive ICP monitoring (adjusted OR: 0.39, 95% CI: 0.17 – 0.83) and Glasgow Coma Scale on ICU admission (adjusted OR: 0.6, 95% CI: 0.52 – 0.69) were significantly associated with in-hospital mortality (Table 3).

In the survival rate analysis, the patients with severe hyponatremia had the worst survival rate among the overall patients. However, there were no significant differences in the mortality rates of patients according to the severity of hyponatremia ($p = 0.430$, Fig. 2).

DISCUSSION

In this study, we investigated the impact of hyponatremia on in-hospital mortality of neurocritically ill patients. Major findings of this study were as follows. First, based on our findings, approximately one-third of the neurocritically ill patients had hyponatremia during their ICU stay. However, there was no significant difference in in-hospital mortality between the no hyponatremia group

and the hyponatremia group. There were also no significant differences in the clinical outcome among the hyponatremia severity based. On the other hand, the length of ICU stay was longer in the hyponatremia group than in the no hyponatremia group. Although hyponatremia did not show significant association with clinical outcomes in the univariable analysis, severe hyponatremia showed significant association with mortality in multivariable analysis. In addition, the multivariable analysis revealed that severe hyponatremia, malignancy, continuous renal replacement therapy, invasive ICP monitoring, and Glasgow Coma Scale on ICU admission were significantly associated with in-hospital mortality.

Hyponatremia is the most common electrolyte abnormality in hospitalized patients³⁾ and especially the neurocritically ill patients⁹⁾; previous studies reported hyponatremia in up to 38 % of critically ill patients and up to 50 % of neurosurgical patients^{2,7,9,16,19)}. Although the pathophysiology of hyponatremia in neurocritically ill patients is multifactorial, cerebral salt wasting syndrome and syndrome of inappropriate antidiuretic are the most common causes of hyponatremia in these patients^{6,9,13)}. Hyponatremia has been associated with the clinical progress of neurocritically ill patients^{9,13,15)}. Acute hyponatremia can cause brain edema and rapid neurological deterioration by increasing the osmotic gradient between the cerebral interstitial tissue and serum⁹⁾. If prolonged, hyponatremia even in mild cases can lead to increased in-

Table 2. Clinical outcome according to the severity of hyponatremia

Variable	No hyponatremia (n = 544)	Mild (n = 257)	Moderate (n = 73)	Severe (n = 29)	p value
In-hospital mortality	48 (8.8)	25 (9.7)	5 (6.8)	5 (17.2)	0.406
28-day mortality	43 (7.9)	17 (6.6)	4 (5.5)	2 (6.9)	0.841
ICU mortality	29 (5.3)	14 (5.4)	3 (4.1)	2 (6.9)	0.948
ICU length of stay (hour)	43.4 ± 201.9	86.0 ± 297.4	49.9 ± 31.7	49.8 ± 36.7	0.092
Hospital length of stay (day)	141.8 ± 89.3	268.6 ± 317.5	295.7 ± 215.4	370.5 ± 261.3	< 0.001

Data are presented as numbers (%) or means ± standard deviations. ICU: intensive care unit.

Table 3. Multivariable analysis of in-hospital mortality according to the severity of hyponatremia

Variable	Adjusted odds ratio (95% CI)*	p value
Hyponatremia		
No hyponatremia	1	Reference
Mild hyponatremia	0.92 (0.45 – 1.85)	0.818
Moderate hyponatremia	0.54 (0.12 – 1.87)	0.368
Severe hyponatremia	5.41 (1.23 – 20.54)	0.017
Malignancy	3.45 (1.29 – 9.72)	0.016
Continuous renal replacement therapy	6.15 (1.65 – 23.38)	0.007
ICP monitoring	0.39 (0.17 – 0.83)	0.019
Glasgow Coma Scale on ICU admission	0.60 (0.52 – 0.69)	< 0.001

CI: confidence interval, APACHE: Acute Physiology and Chronic Health Evaluation, ICP: intracranial pressure, ICU: intensive care unit.

*Adjusted for hyponatremia, age, sex, comorbidities, cause of ICU admission, utilization of organ support modalities, use of invasive ICP monitoring device, hyperosmolar therapy, and APACHE II score.

Fig. 2. Kaplan Meier curves of in-hospital mortality according to hyponatremia severity.

tracranial pressure, neurological abnormalities, and even death^{4,9}. Some complications, such as hyponatremic seizures, are more prevalent in severe cases of hyponatremia than in benign disease⁹. For instance, the clinical manifestations of hyponatremia are severe in neurocritically ill patients with intractable intracranial hypertension, severe brain damage, or neurosurgical intervention^{6,16}.

Similar to the previous reports, in this study, hyponatremia was also a common electrolyte abnormality in neurocritically ill patients. However, most hyponatremia cases were mild and only 3% of all patients showed severe hyponatremia. In the present study, severe hyponatremia was a significant predictor of in-hospital mortality, while mild to moderate hyponatremia were not associated with clinical outcomes. However, these findings are inconsistent with previous studies^{6,16}. Even patients with normal sodium level or hyponatremia were excluded from this study if they had a history of hypernatremia during ICU hospitalization. Several studies revealed that hypernatremia was associated with poor clinical outcomes in neurocritically ill patients^{8,10,11,18}. Although hyperosmolar therapy is the standard approach to the treatment of intracranial hypertension in the neurocritically ill patients, it is associated with hypernatremia and hyperosmolar therapy-induced acute kidney injury that can aggravate hypernatremia^{1,11,18}. In addition, hypothalamic dysfunction due to brain injury can contribute to hypernatremia^{12,18}. Therefore, ICU-acquired hypernatremia is a possible complication in severe brain injuries. For this study, it is possible that some patients with severe brain injuries were excluded due to accompanied hypernatremia.

This study has several limitations. First, this was a retrospective review of medical records using data extracted from a Clinical Data Warehouse. The nonrandomized nature of registry data might

have resulted in a selection bias. Second, the duration of hyponatremia and correction of serum sodium was not reflected in this study. Third, most hyponatremia cases were mild with only a small percentage of severe hyponatremia cases. Finally, the distribution of neurosurgical diseases was different from that in the general neurosurgical ICU, and the proportion of patients with brain tumors was particularly high.

CONCLUSIONS

Based on our study findings mild to moderate hyponatremia were not associated with clinical outcomes in neurocritically ill patients. However, severe hyponatremia was significantly associated with in-hospital mortality. Therefore, adequate and timely regulation of serum sodium level is important for favorable prognosis and survival of neurocritically ill patients.

NOTES

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Informed Consent

The requirement for informed consent was waived due to the retrospective nature of this study.

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