PREDICTORS OF OUTCOME IN HOSPITALIZED PATIENTS WITH SEVERE HYPONATREMIA

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Severe hyponatremia is associated with increased morbidity and mortality. Clinicians treating patients with severe hyponatremia are often torn between a desire to promptly raise serum sodium concentration to a "safe range," and at the same time, to avoid excessively rapid correction of hyponatremia. The aim of this study was to assess the prevalence of severe hyponatremia in hospitalized patients, the etiologic factors involved, as well as treatment and outcome of the patients using a retrospective case series.

Methods: Retrospective study of 168 patients with severe hyponatremia (<115mmol/L) seen at Grady Memorial Hospital, a tertiary teaching hospital, in Atlanta, Georgia, from 1997-2001. The main outcome measures of interest were death during admission or occurrence of neurologic symptoms before, during or after therapy.

Results: One hundred sixty-eight patients met the inclusion criteria out of a total of 5994 patients with hyponatremia treated at our hospital over the study period. Eighty-nine patients (52.9%) were symptomatic. The mean absolute serum sodium at 48-hours of therapy was 120.02+ -8.31 mmol/L. Respiratory failure and/or hypoxia was present in 28 patients (16.7%); sepsis was documented in 16 patients (9.5%). Mortality rate was high, 34 patients died (20.2%). On multivariate analysis factors with strong association with mortality of patients with severe hyponatremia were hypoxia, presence of neurologic symptoms, slow correction rates and a diagnosis of sepsis.

Conclusions: The mortality associated with severe hyponatremia remains high. Sepsis, respiratory failure and the presence of symptoms predict poor outcome in hospitalized patients with severe hyponatremia. More aggressive therapy with 3% saline may improve outcome in symptomatic patients. Our data suggest that a slow rate of correction in severe hyponatremia is associated with higher mortality than rapid correction, at least in the short term. (*J Natl Med Assoc.* 2003;95:335-343.)

Key words: Hyponatremia ♦ correction ♦ symptoms ♦ sepsis ♦ mortality

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Hyponatremia is the most common electrolyte disorder in clinical medicine.[1] Severe hyponatremia, defined as a serum sodium concentration of less than 115 mmol/L, may be associated with substantial morbidity and increased mortality.[2,3] However, considerable controversy surrounds the optimal therapy for severe hyponatremia, as both an overly rapid correction rate and slow correction may be

Table 1.

Demographic Characteristic		*P* Value
Age Mean~ SD	52.1 ~ 17.4	0.16
Sex (%)		
Men	96	0.86
Women	72	
Race (%)		
Black	156	0.65
White	9	
Other	3	
Location:		
ICU	31	
Medical Floor	137	
History of Alcoholism #(%)	40 (23.8%)	0.39
#Taking HCTZ	27 (16.7%)	
Symptomatic	89 (52.97%)	
Asymptomatic	79 (47.02%)	
# of Patients who had Chest Radiograp	145(86%)	
# of Patients with Cerebral Imaging	40(23.8%)	

associated with neurologic injury and death.[4-7] Ayus et al. proposed an hourly correction rate of 1.3mmol/L, using 5% saline with furosemide, while avoiding correction to normonatremic or hypernatremic levels at 48 hours, or a correction of no greater than 25mmol/L in the first 48 hours.[5] Sterns and his coworkers, on the other hand, suggest that patients with severe chronic hyponatremia are more likely to avoid neurologic complications when hyponatremia was corrected slowly.[4,6,7] Furthermore, it appears that chronic hyponatremia is not an entirely benign condition, as a recent report has shown that chronic symptomatic hyponatremia in post-menopausal women can be associated with major morbidity and mortality.[8]

Unresolved at this time is whether the patients die of hyponatremia, the effects of therapy, or co-morbid disease. In this report, we describe the etiologic factors, incidence, therapy, and outcome of severe hyponatremia in hospitalized patients and characterize the factors affecting mortality in this patient population.

METHODS

Study Setting

This study was done at Grady Memorial Hospital, a large tertiary teaching hospital , that serves a mostly urban population of city of Atlanta and the surrounding counties of Dekalb and Fulton.

Study Design

A retrospective review of patients identified from archived laboratory data using a computerized laboratory information system. All definitions and diagnostic criteria were defined prospectively.

Population

Over a four-year period (January 1, 1997 to February 2001), we identified 182 patients with a serum sodium concentration of 115mmmol/L or less seen at this hospital using a computerized laboratory information systems (LIS) database. Two patients in the pediatric age group (<14 years) were excluded. In six patients, repeat serum sodium data were in normal range and these cases were considered to be spurious and, therefore, excluded since no specific therapy was given by the treating physicians. In four other patients, data concerning fluid administration and oxygenation status during hyponatremia were incomplete and these were excluded as well. Finally, two more patients were excluded, because hyponatremia was documented in the emergency room, but admission and follow-up

data were unavailable.

A total of 168 patients were then selected for inclusion into the study. The medical records of these patients were reviewed by two of us (HBB and CMN) to obtain data on demographics, laboratory findings, fluid therapy, symptoms of hyponatremic encephalopathy before and after therapy, and outcome using a data abstraction form. Over the study period, 5994 patients at this hospital received the International Classification of Diseases (ICD-9) code for hyponatremia -276.1.

Serum sodium, and urine sodium were measured using a Hitachi 747-200 analyzer (Boehringer Manheim, Indianapolis), while Osmolarity was measured by freezing point depression. Determination of the causes of hyponatremia was based on the opinion of the treating physician and/or nephrologist consulted on the case. The rate of correction of hyponatremia in the first 24 hours was derived by assessment of changes in serum sodium (measured at least twice daily in all patients), over time. Absolute levels of serum sodium after 48 hours of therapy also were noted. The comorbid factors in these patients on admission were recorded on a data abstraction sheet.

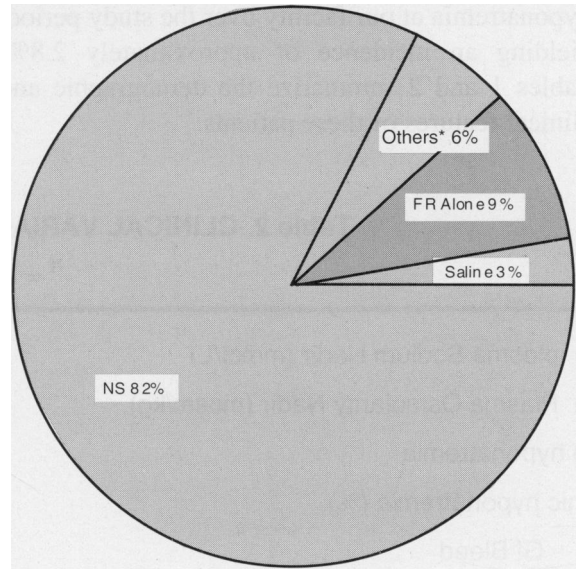
DEFINITIONS

Hyponatremia was defined as acute if the duration was less than 48 hours, and chronic if the duration was longer than 48 hours,[8-10] or if previous laboratory data document hyponatremia in the preceeding days or months that was not completely corrected prior to hospital discharge. Correction of hyponatremia was judged to be overly rapid if an increase of > 25mmmol/L in 48 hours occurred, or if correction to hypernatremic levels occurred over the same time.[5,12] A diagnosis of hyponatremia was made by our hospital laboratory for patients with a serum sodium of less than 133mmol/L.

Hypoxia was defined by a partial pressure of oxygen (PaO_2) < 60mmHg on arterial blood gas or pulse oximetry showing oxygen saturation of <90% during the first 24 hours of admission with hyponatremia.

Sepsis was defined by the presence of fever (temperature >100.5° F) or hypothermia in association with tachycardia, tachypnea and leukocytosis with a suspected or confirmed site of infection.[13] The presence of symptoms such as nausea and vomiting, dizziness, altered mentation or seizure activity[14,15] were attributed to hyponatremic encephalopathy, unless there was a coexisting medical condition (such as hypoglycemia), or medication effect to account for these symptoms, and especially if the symptoms improved with correction of hyponatremia. Chest radiographic and cerebral imaging data (computed tomographic or magnetic resonance scans) also were reviewed.

Figure 1. FLUID PRESCRIPTION TO CORRECT HYPONATREMIA IN OUR STUDY POPULATION



ANALYSIS

Data for continuous measurements are expressed as mean + or – (±) SD. The primary outcome of interest was short-term mortality during admission with severe hyponatremia. Differences across demographic, clinical, and treatment characteristics were assessed for asso-

ciation with death using chi-square or student's *t* test. In separate logistic regression models that included all the studied risk factors, we evaluated the relationship of these variables to outcome. A *P* value of <0.05 was considered significant. The associations of identified variables were further reported as odds ratios. Data were analyzed using the SAS package (SAS Cary, NC).

RESULTS

Demographic and Clinical Characteristics of Study Patients

We found severe hyponatremia in 168 patients out of a total of 5994 patients with a diagnosis of hyponatremia at our facility over the study period, yielding an incidence of approximately 2.8%. Tables 1 and 2 summarize the demographic and clinical features of these patients.

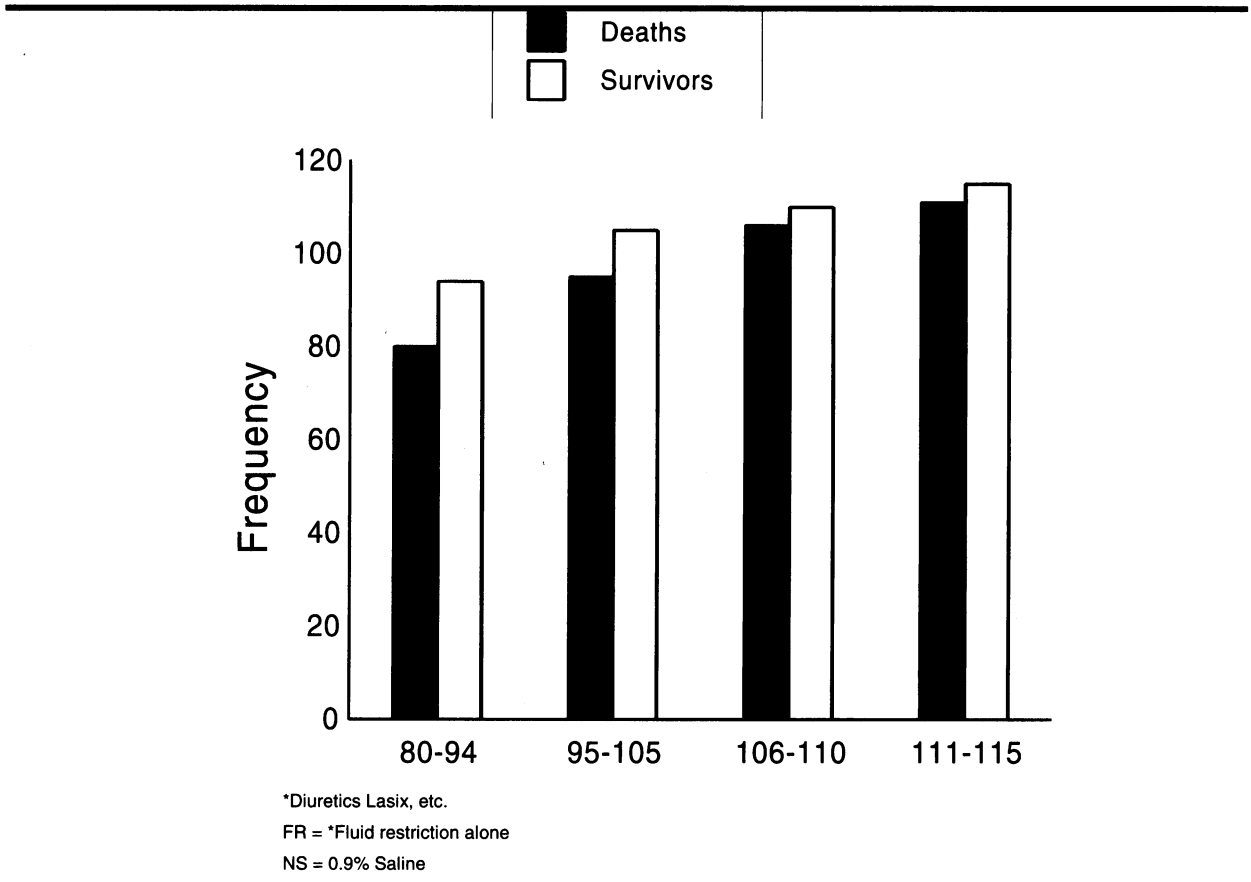
The mean age (SD) of the 168 patients (96 men, 72 women) was 52.1 ± 17.4 years. The patients were predominantly black (92.8%), and 81.54% were admitted to the internal medicine floor service, while 18.45% were managed in the intensive care unit (ICU). One hundred thirty-eight patients (82.14%) had acute hyponatremia, 28 patients (16.67%) had chronic hyponatremia, and for two patients it could not be determined if hyponatremia was acute or chronic. Symptoms of hyponatremic encephalopathy were present in 89 patients (52.97%), while 79 patients (47.02%) had no documented symptoms. Of the symptomatic patients, altered sensorium was documented for 46 patients (51.7%); seizures for 20 patients (22.5%); nausea and vomiting for eight patients (4.8%); two patients were comatose (2.2%); dysarthric speech was noted in two patients (2.2%); while gaiet disturbance and frequent falls occurred with six

Table 2. CLINICAL VARIABLES AND COMORBIDITY

N = 168

Mean plasma Sodium Nadir (mmol/L)	109̃ (5.5)
Mean Plasma Osmolarity Nadir (mosm/kg)	242.4̃ (26.1)
Acute hyponatremia	140 (83.3%)
Chronic hyponatremia (%)	28(16.7%)
GI Bleed	5(2.9%)
Diabetes # (%)	40 (23.8%)
Congestive heart failure # (%)	20 (11.9%)
Renal Failure # (%)	15 (8.9%)
Cirrhosis # (%)	12 (7.14%)
Sepsis # (%)	16 (9.5%)
COPD	9 (5.4%)
Hypoxia/or resp. failure # (%)	28 (16.7%)
Pulmonary Edema on Chest X-Ray	25 (14.8%)
Rate of correction in 1st 24 hours	0.869̃ (26.1)
Mean Na at 48 Hours	127.086̃ (7.913)
HIV # (%)	34(20.23%)

Figure 2. HISTOGRAM SHOWING DISTRIBUTION OF PLASMA NA NADIR IN SURVIVORS AND DEATHS FROM SEVERE HYPONATREMIA



patients (3.6%). Symptoms were present in nine patients with chronic hyponatremia (32.14%), and 80 patients with acute hyponatremia were symptomatic (89.9%).

Diabetes Mellitus was the most common comorbid condition present in 40 patients (23.8%), while 34 patients (20.2%) had human immunodeficiency virus infection (HIV). Hypoxia was documented in 28 patients (16.7%), while 16 patients (9.5%) had a diagnosis of sepsis.

Hypovolemia was an etiologic factor of hyponatremia in 39 patients (23.21%), while 30 patients (17.9%), had a clinical picture compatible with the syndrome of inappropriate antiduretic hormone secretion (SIADH). Other factors causing hyponatremia in this study population included congestive heart failure (10.1%), use of thiazide diuretics (7%), cirrhosis (6%), psychogenic polydipsia in 2.3%, rapid administration of hypotonic fluids, along with use of morphine and non-steroidal anti-inflammatory drugs to treat sickle-cell pain crisis patients (5.95%). Endocrine causes contributed to hyponatremia in six patients (3.5%), two patients with hypothyroidism, three patients with adrenal insufficiency, and one patient with panhypopituitarism. Multiple factors contributed to hyponatremia in 18 patients (10.9%).

There was no association between the demographic variables, cause of hyponatremia, admission to ICU, or HIV status and outcome. Similarly, there was no relationship between serum sodium nadir (index of severity) and survival, as shown in Figure 2. Whether hyponatremia was acute vs. chronic did not affect mortality (p=0.297).

Correction of Hyponatremia and Outcome

Figure 1 summarizes fluid prescription to correct hyponatremia in our study population. The total of 137 patients (82%) received normal saline during correction of hyponatremia, while hypertonic (3%) saline was used in only 12 patients (7.14%). Restriction of hypotonic fluids was imposed on all but one patient. The mean hourly rate of correction in the first 24 hours was 0.8mmol/L. The mean absolute serum sodium concentration after 48 hours of therapy (available in 110 patients; 65.5%), was 120.02 ± 8.31 mmol/L. Overly rapid correction (>25mmol/L/48hours) occurred in 17 patients (15.5%). One of these patients developed a progressive encephalopathic illness from which she died six weeks later. However, her brain autopsy did not reveal any demyelinating lessions to suggest possible osmotic demyelination syndrome.

The overall mortality rate was high -20.2%, and there was a trend towards increasing mortality with a slower rate of correction. The amount of correction at 48 hours, as measured by the absolute serum sodium concentration (127.09 ± 7.91 in survivors vs. 118.83 ± 9.84 in non-survivors), was significantly associated with mortality (p=0.0016). The presence of hypoxia also was strongly associated with mortality in severe hyponatremia (p=0.0001). Other factors with significant association with short-term mortality include a co-morbid diagnosis of sepsis (p=0.0006) and the presence of symptoms (p=0.0032) (see Table 3). Neither the presence of hypokalemia nor a history of alcoholism affected mortality (p=0.948 and 0.392, respectively.)

DISCUSSION

The major aim of this study was to assess the outcome of severe hyponatremia and characterize factors influencing outcome in hospitalized patients with this disorder. This study suggests that severe hyponatremia is associated with high mortality. It is unclear if this association derives from hyponatremia per se, or the associated co-morbidity in these subjects.

One of the major patient characteristics associated with increased mortality was the presence of symptoms. Our data fails to confirm a previous association of hyponatremia in general with increased mortality in HIV-infected patients,[16] CHF,[17] thiazide diuretic use[18] and psychogenic polydipsia.[19] Our prevalence data of 2.8% supports previous observations showing that severe hyponatremia is indeed quite rare.[20] A recent study found an incidence of 1% among South African patients.[21] Even though mortality did not differ across etiologic groups, morbidity differences were observed between etiologic groups of patients. While morbidity was 100% in patients with psychogenic polydipsia, mortality

Table 3. MULTIVARIATE ANALYSIS OF ASSOCIATION OF SELECTED FACTORS WITH MORTALITY

Variable	Mortality Odds Ratio (%)	P*
Hypoxia	13.457 (4.7-38.4)	<0.0001
Rate of Correction (hourly)	0.334 (0.126-0.883)	0.027
Sodium at 48 Hours	3.59	0.0012
Sepsis	8.623 (2.11-35.16)	0.002
Presence of Symptoms	3.038 (1.08-8.5)	0.035

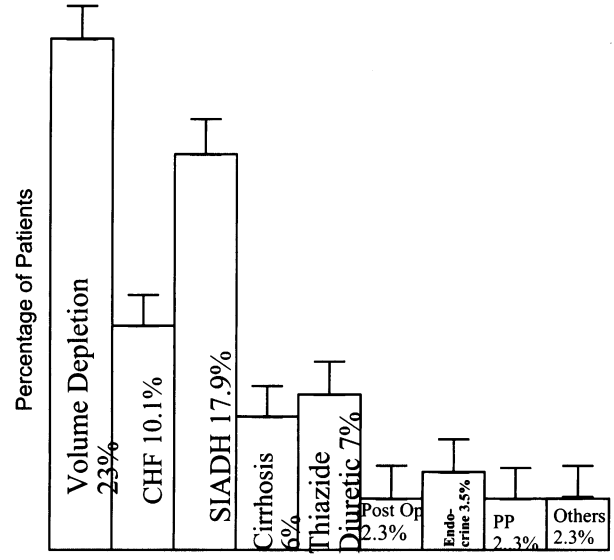
was zero in this group.

Patients in sickle-cell pain crisis who developed acute hyponatremia following rapid administration of 5% dextrose in water, therapy with morphine and NSAIDS (for pain control) also had 100% survival with only 10% morbidity. While mild, induced hyponatremia appears beneficial in therapy of sickle cell crisis, as it causes swelling of red blood cells which helps correct the sickling effect,[22,23] our data shows that this therapy, when combined with morphine and NSAIDS which impair water excretion,[24] can cause severe hyponatremia. This study is the first to document the association between therapy for sickle-cell crisis and the occurrence of severe hyponatremia.

Another major finding of this study was the association of slow rates of correction with mortality. Our data supports previous observations by Ayus et al. that a slow correction rate (<0.7mmol/L/hour) was associated with high mortality.[5] Overall, our study revealed a reluctance to use hypertonic saline in symptomatic patients with severe hyponatremia. The reasons for this reluctance are unknown. One possible explanation could be a desire to avoid overly rapid correction. Another explanation could be the high proportion of patients in our study population with hypovolemia, in whom normal saline may be considered adequate therapy. However, this would be an inadequate explanation, as normal saline also was prescribed to symptomatic patients with SIADH, leading to worsening of hyponatremia, and uncal herniation in one patient with tuberculous meningitis. The safety of hypertonic saline in symptomatic patients is well established.[25-27]

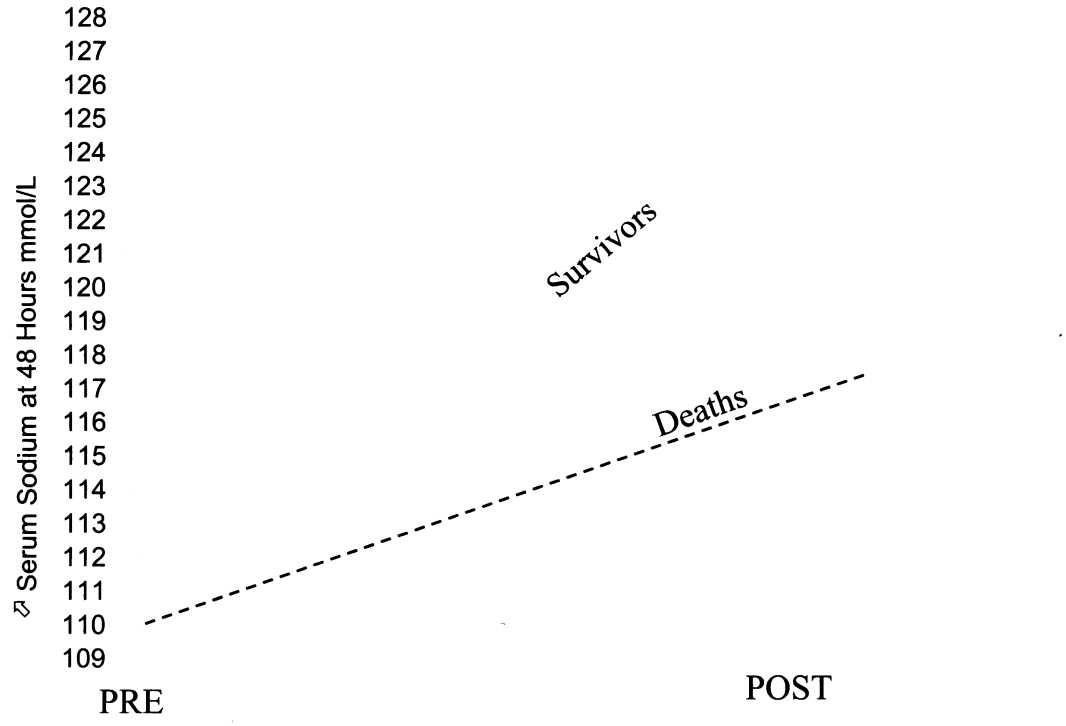
Our finding of an association between hypoxia and mortality in hyponatremia has been previously observed by others.[28-31] The precise basis for this association between hypoxia and mortality in hyponatremia is unclear, but some authors suggest that hypoxia plays a critical role in the genesis of hyponatremic brain injury in experimental animals. Vexlar et al. suggest, in fact, that hypoxia may interfere with cerebral adaptive responses to hyponatremia.[30] Our definition of hypoxia in this study was fairly liberal, and yet this association remained very strong. Recently Ayus et al. reported on the occurrence of pulmonary edema in marathon runners with hyponatremia.[32] In our series, pulmonary edema was found in only 25 patients (14.8%). Death in one patient was clearly associated with overly rapid correction. Interestingly, this patient was treated with fluid restriction alone. That fluid restriction alone can lead to overly rapid correction has been reported by other investigators.[33] This suggests that clinical vigilance is still vital when a severely hyponatremic patient is managed with fluid restriction alone.

Figure 3. Etiologic Factors of Severe Hyponatremia (N = 168)



This study also revealed an association between sepsis and increased mortality in severe hyponatremia. This was intriguing, since none of these patients were in frank septic shock, or had evidence of multi-organ systems failure at the outset. The mechanism by which sepsis would increase mortality with severe hyponatremia is unknown. Some data suggest that alterations of arginine vassopressin levels may occur in sepsis, though results have been variable depending on the phase of sepsis studied.[34] Others have previously noted the association of sepsis with increased mortality in hyponatremia.[35-37]

Figure 4. EFFECT OF CORRECTION RATES ON SURVIVAL (Absolute Na at 48 hours mmol/L)



One possible explanation for the association between sepsis and increased mortality in hyponatremia is the interference with the Na^+K^+ ATPase, an enzyme involved in early cerebral adaptation to hyponatremia.[38] Furthermore, there are suggestions that hyponatremia during sepsis is associated with progressive failure of the energy-dependent transport involving this enzyme.[36]

Though our study has the unique strength of being one of the largest studies of outcome of severe hyponatremia in hospitalized patients, it has some important limitations. Firstly, the retrospective, observational nature of our study, and the sample size limits the robustness with which we can analyze the data, and hence limits the power of some of our observations. Second, by evaluating patients with severe hyponatremia, an unintended element of bias is introduced. Third, our patients had a predominance of acute severe hyponatremia and the applicability of our findings to the general population of patients with hyponatremia is unknown. In spite of these limitations, our findings are noteworthy, and prospective studies would be needed to validate these findings. In conclusion, this study has shown that severe hyponatremia in hospitalized patients is associated with high mortality. Hypoxia, symptoms of encephalopathy, slow correction rates and sepsis appear to increase mortality.

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