Prognostic impact of hyponatremia occurring at various time points during hospitalization on mortality in patients with acute myocardial infarction

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Abstract
We investigated the incidence and prognostic impact of hyponatremia occurring at various time points during hospitalization on long-term mortality in acute myocardial infarction (AMI) survivors. We retrospectively studied 1863 patients diagnosed with AMI. Baseline, nadir, and discharge sodium levels during hospitalization were recorded and analyzed. Hyponatremia was defined as a serum sodium level <135 mEq/L. On the basis of baseline, nadir, and discharge sodium levels during hospitalization, hyponatremia was diagnosed in 309 (16.6%), 518 (27.8%), and 147 (7.9%) patients, respectively. In a multivariate Cox-proportional regression analysis, discharge sodium level had the strongest significant relationship with long-term mortality (hazard ratio [HR] as continuous variable = 1.06, 95% confidence interval [CI]: 1.01–1.11, P = .026; HR as categorical variable = 1.71; 95% CI: 1.06–2.75; P = .028), but baseline and nadir sodium had no prognostic impact on long-term mortality after adjustment. The serum sodium level and incidence of hyponatremia varied at different time points during hospitalization. In addition, the association between sodium level and long-term mortality differed at these various time points. The discharge sodium level, among the various time points, seems the best predictor of long-term mortality in AMI survivors.

Abbreviations: ACE = angiotensin converting enzyme, AMI = acute myocardial infarction, ARB = angiotensin receptor blocker, AUC = area under the receiver operating characteristic curve, BMI = body mass index, CI = confidence interval, eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, NSTEMI = non-ST-segment elevated MI, ROC = receiver operating characteristic, STEMI = ST-segment elevated MI.

Keywords: hypotremia, mortality, myocardial infarction, time point

1. Introduction

Hyponatremia, defined as serum sodium levels <135 mEq/L, is the most frequently encountered electrolyte abnormality in hospitalized patients and has been considered a marker of underlying disease severity and prognosis in diverse clinical settings.[1-4] Hyponatremia is also an important predictor of mortality in patients with acute myocardial infarction (AMI).[5-10] In AMI, hyponatremia is associated with complex neurohormonal activation, involving nonosmotic release of vasopressin and activation of the sympathetic nervous system and renin-angiotensin-aldosterone system.[11-14] These mechanisms have a potentially negative impact on survival in these patients.[6]

During periods of hospitalization, the neurohormonal activation can be mediated by factors such as the restoration of flow in the stenosed artery, and this is especially important in the era where primary angioplasty is a preferred method of primary management of AMI.[15] In addition, pharmacologic interventions such as β-blocker, angiotensin converting enzyme (ACE) inhibitor, and angiotensin receptor blocker (ARB) also attenuate neurohormonal activation.[16-18] Therefore, many patients who survive the acute event may show altered serum sodium levels during the hospitalization period.

Owing to the clinical usefulness of hyponatremia as a marker of AMI severity and prognosis, it is important to assess the influence of hyponatremia at various time points during hospitalization. However, the prognostic consequences of the changes in serum sodium levels in patients with AMI have not been investigated. We therefore undertook this study to assess the prognostic impact of hyponatremia occurring at various time points during hospitalization on long-term mortality in survivors of AMI. We documented baseline, nadir, and discharge serum sodium levels during hospitalization and evaluated the relationship between the presence of hyponatremia and long-term mortality.
2. Methods

2.1. Study population

We conducted a retrospective evaluation of 2289 patients admitted to the emergency department of Chonnam National University Hospital between January 2006 and October 2009 with a diagnosis of myocardial infarction (MI). Of these patients, 118 who died during hospitalization and 308 who did not have at least 2 serum sodium level measurements during hospitalization were excluded from the study, leaving a total study population of 1863 patients. Demographic, clinical, laboratory, and treatment data were obtained from the hospital’s computerized database.

AMI was diagnosed based on the typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase MB fraction) of biochemical markers of myocardial necrosis with at least one of the following: ischemic symptoms, development of pathologic Q waves on the electrocardiogram, electrocardiogram changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention. AMI was subcategorized into ST-segment elevated MI (STEMI) and non-STEMI (NSTEMI). STEMI was defined as the presence of new ST-segment elevation of at least 1 mm (0.1 mV) in continuous leads or new left bundle-branch block on the index or electrocardiogram. NSTEMI was manifested by ST-segment depression or T wave inversion with corroborating laboratory evidence of infarction. Left ventricular ejection fraction (LVEF) was measured using bidimensional echocardiography from 2- to 4-chamber apical views by the modified Simpson method.

This study was approved by the institutional review board of Chonnam National University Hospital, Gwangju, and Republic of Korea (CNUH-2012-148). The study was performed in accordance with the tenets of the Declaration of Helsinki of 1975, as revised in 2000. Each patient in the present study was informed about data usage for this investigation. However, since this study was a retrospective medical record-based study and the study subjects were deidentified, the institutional review board waived the need for written patient consent.

2.2. Definition of hyponatremia and renal function assessment

Hyponatremia was defined as a serum sodium level <135 mEq/L. The severity of hyponatremia was defined as mild (130–135 mEq/L) and moderate-to-severe (<130 mEq/L). Serum sodium levels were documented as follows: baseline, measured at the day of admission; nadir, the lowest sodium level measured during hospitalization; and discharge, the last sodium level measured during hospitalization. Renal function assessment was based on estimated glomerular filtration rate (eGFR). The Chronic Kidney Disease Epidemiology Collaboration equation calculates eGFR as follows: eGFR in mL/min/1.73 m² = 141 × minimum (creatinine/κ, 1)° × maximum (creatinine/κ, 1)° × 0.9934(kg/m²) × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for women and 0.9 for men and α = −0.329 for women and −0.411 for men.

2.3. Treatment

Reperfusion strategies consisted of percutaneous angioplasty and intravenous thrombolytic therapy. The choice of treatment strategies was decided by the clinicians performing these interventions according to the American College of Cardiology and the American Heart Association guidelines for the management of patients with acute coronary syndrome. During their hospitalization, patients received evidence-based medical treatment that included aspirin, clopidogrel, β-blocker, ACE inhibitor, ARB, and statins, which were prescribed in a nonrandomized unselected condition.

2.4. Clinical end points

The primary end point of the study was 3-year mortality after MI. Assessment of the survival status and validation of clinical outcomes were performed by collecting records from the outpatient clinic or by follow-up telephonic interviews.

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Baseline characteristics between the groups were compared using Student t test for continuous variables and Pearson chi-square test or Fisher exact for categorical variables. The 3-year mortality was estimated by the Kaplan–Meier method, and curves were compared with the log-rank test. The relationship between hyponatremia at various time points during hospitalization and 3-year mortality was assessed by univariate and multivariate Cox proportional regression analyses. The variables for adjustment were selected on the basis of factors known to be associated with all-cause mortality in patients with AMI and the results of the statistically significant univariate analysis (P < .1). The variables included in the analyses were age, sex, body mass index (BMI ≥ 25 kg/m²), comorbidities (hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia), smoking status, Killip classification, LVEF (<45%), diagnosis (STEMI vs NSTEMI), eGFR on admission (<60 mL/min/1.73 m²), reperfusion strategy (angioplasty and thrombolysis), and medical treatments during hospitalization. One of the 3 sodium levels, baseline, nadir, and discharge sodium levels, were entered into the Cox proportional regression analysis model as either continuous or categorical variables. To compare the incremental prognostic value of the 3 sodium levels, we assessed area under the receiver operating characteristic (ROC) curves (AUC) using Harrel C index. The same variables, which were entered into Cox proportional regression analysis, were used for adjusting confounders. Since hyponatremia is related to heart failure and impaired renal function, which are common concomitants of AMI, we stratified the study population into 4 groups based on the presence or absence of reduced ejection fraction (LVEF <45%) or impaired renal function (eGFR < 60 mL/min/1.73 m²). The variables noted above, with the exception of LVEF, were used for adjusted Cox proportional regression analysis. The study population was similarly divided into 4 groups based on the presence or absence of hyponatremia and impaired renal function and the same variables were used, except for eGFR on admission.

All statistical tests were 2-tailed, and P < .05 was considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences software, version 22 (IBM SPSS Statistics, IBM, Armonk) and AUC comparisons were made using SAS software version 9.12 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 1863 patients (mean age, 63.6 ± 12.8 years; men, 70.4%) were included in the present study. The clinical characteristics of patients with normal serum sodium or hyponatremia at admission are shown in Table 1. Hyponatremia...
Table 1
Baseline characteristics of according to hyponatremia at admission.

|                  | Normal (n=1554) | Hyponatremia (n=309) | P   |
|------------------|-----------------|----------------------|-----|
| Age, y           | 63.2±12.7       | 65.5±12.7            | .003|
| Male, %          | 1110 (71.4%)    | 201 (65.0%)          | .025|
| BMI, kg/m²       | 24.2±3.1        | 23.6±3.0             | .001|
| Risk factors     |                 |                      |     |
| Hypertension     | 727 (46.8%)     | 175 (56.6%)          | .002|
| Diabetes mellitus| 370 (23.8%)     | 141 (45.6%)          | .001|
| Coronary artery disease | 195 (12.5%) | 46 (14.9%) | .263|
| Hyperlipidemia   | 72 (4.6%)       | 13 (4.2%)            | .741|
| Smoking          | 947 (60.9%)     | 175 (56.6%)          | .158|
| Initial presentation |             |                      |     |
| SBP              | 130±30          | 131±26               | .406|
| DBP              | 81±18           | 82±15                | .383|
| HR               | 75±18.8         | 79.7±17.5            | .001|
| LVEF, %          | 55.0±12.3       | 52.3±13.2            | .001|
| Killip class     |                 |                      |     |
| I                | 1206 (77.6%)    | 201 (65.0%)          | .001|
| II               | 163 (10.5%)     | 37 (12.0%)           |     |
| III              | 122 (7.7%)      | 54 (17.5%)           |     |
| IV               | 63 (4.1%)       | 17 (5.5%)            |     |
| Renal function   |                 |                      |     |
| Serum creatinine, mg/dL | 1.06±0.90     | 1.42±1.69            | <.001|
| eGFR             | 79.2±23.5       | 69.3±28.8            | <.001|
| Laboratory finding |               |                      |     |
| Maximal CK       | 1315±1877       | 1308±1783            | .950|
| Maximal CK-MB    | 189±113         | 79±108               | .331|
| Maximal troponin I | 57±99         | 51±75                | .356|
| Maximal troponin T | 4.6±7.1      | 5.3±9.4              | .177|
| Diagnosis        |                 |                      |     |
| STEMI            | 928 (59.7%)     | 177 (57.3%)          | .426|
| NSTEMI           | 626 (40.3%)     | 132 (42.7%)          |     |
| Reperfusion strategies |             |                      |     |
| Angioplasty      | 1332 (87.5%)    | 258 (84.5%)          | .336|
| Thrombolysis     | 124 (8.0%)      | 11 (3.6%)            | .006|
| In-hospital medication |            |                      |     |
| Aspirin          | 1540 (99.1%)    | 308 (99.7%)          | .300|
| Clopidogrel      | 1526 (98.2%)    | 305 (98.7%)          | .531|
| Anticoagulant    | 1539 (99.0%)    | 306 (99.0%)          | .993|
| Beta-blocker     | 1331 (85.6%)    | 265 (85.8%)          | .960|
| Calcium channel blocker | 176 (11.3%) | 28 (9.1%) | .244|
| ACE inhibitor or ARB | 1400 (90.1%) | 273 (86.3%) | .356|
| Statin           | 1101 (70.6%)    | 216 (69.9%)          | .738|
| Diuretics        | 455 (29.3%)     | 124 (40.1%)          | <.001|
| Loop diuretics   | 396 (25.5%)     | 119 (38.8%)          | <.001|
| Thiazide         | 60 (3.9%)       | 14 (4.6%)            | .571|
| Spironolactone   | 188 (12.1%)     | 58 (18.9%)           | .001|

ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, CK = creatine kinase, CK-MB = creatine kinase MB fraction, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HR = heart rate, LVEF = left ventricular ejection fraction, NSTEMI = non-ST-segment elevated MI, SBP = systolic blood pressure, STEMI = ST-segment elevated MI.

was associated with older age, female gender, lower BMI, and history of hypertension or diabetes mellitus. Compared to patients with normal serum sodium, those with hyponatremia had higher Killip classification, lower LVEF, higher serum creatinine, and lower eGFR on admission and were more likely to receive thrombolytic therapy during hospitalization. There was no difference in peak cardiac enzyme levels and pharmacologic therapy administered during hospitalization with the exception of loop diuretics and spironolactone, which were more commonly prescribed in patients with hyponatremia at admission.

3.2. Incidence of hyponatremia throughout the hospitalization period

Hyponatremia was present in 309 (16.6%) patients on admission, with mean baseline serum sodium levels of 137.5±3.5 mEq/L. Figure 1 shows changes in serum sodium level during hospitalization. The mean nadir sodium level was significantly lower than the baseline level (mean, 135.8±3.3 mEq/L; P <.001), and the number of patients with hyponatremia increased to 318 (27.8%). The discharge sodium level was higher than nadir (P <.001), and the number of patients with hyponatremia significantly decreased to 147 (7.9%).

3.3. Multivariate analysis for long-term mortality

The patients were followed up for a mean period of 3.72±1.86 years. The duration of follow-up was right-censored at 3 years for Kaplan–Meier and Cox-proportional regression analysis. A total of 191 (10.3%) patients died during the follow-up period. Kaplan–Meier curves for crude 3-year cumulative mortality by serum sodium level at various times are shown in Fig. 2. Patients with hyponatremia had significantly higher mortality compared to patients with normal serum sodium at all time points (P <.001). Table 2 shows unadjusted and adjusted Cox proportional regression analysis for long-term mortality according to each sodium level. There was an inverse unadjusted relationship between baseline sodium level and mortality, but the effect of baseline sodium level on mortality was statistically nonsignificant when adjusted for other clinical variables. Nadir sodium level had a stronger relationship with mortality than did baseline sodium, although statistical significance was not maintained in the adjusted variable analysis model. In contrast, discharge sodium level, as either a continuous or categorical variable, was independently associated with mortality, even after adjustment for other clinical variables. We assessed ROC curves analysis to compare the incremental prognostic value of admission, nadir, and discharge sodium levels. In ROC analysis, there were comparable results among the 3 sodium levels after adjusting for confounders (AUC 0.813, 95% confidence interval [CI] 0.784–0.843; AUC 0.815, 95% CI 0.785–0.844; AUC 0.812, 95% CI 0.784–0.846).

Figure 1. Box and whisker plots of changes in serum sodium level during hospitalization. The line within the box denotes median and the box spans the interquartile range (25%–75%). Whiskers extend from 10% to 90%. * P <.001 compared with baseline sodium level; † P <.001 compared with nadir serum sodium level.
0.815, 95% CI 0.785–0.845, for admission, nadir, and discharge sodium levels, respectively).

For further analysis, the study population was stratified into 4 groups based on presence or absence of reduced ejection fraction (LVEF < 45%) or impaired renal function (eGFR < 60 mL/min/1.73 m²). Hyponatremia was associated with increased mortality risk, regardless of ejection fraction (Fig. 3A). Similar results were observed in patients with normal and impaired renal function (Fig. 3B).

**4. Discussion**

The present study shows that an inverse relationship exists between hyponatremia and long-term mortality among patients surviving AMI. When we defined hyponatremia at various time points during hospitalization, we observed that the prognostic impact of hyponatremia on long-term mortality varied according to the time point during hospitalization. The sodium level at discharge showed the strongest association with adverse clinical outcome and remained an independent predictor of long-term mortality after adjustment for all clinical variables. Nadir sodium levels during hospitalization were also marginally related to adverse clinical outcome, whereas baseline serum sodium had no adjusted prognostic impact on long-term mortality. Numerous studies have evaluated the association between hyponatremia and clinical outcomes in patients with AMI, either STEMI or NSTEMI. [5–10] However, most of these examined the prognostic impact of hyponatremia in the early phase of AMI alone, generally at the time of admission or within the first 72 hours. [5–10] In the present study, we discovered significant time-dependent differences in the clinical impact of hyponatremia on long-term mortality in patients with AMI.

The mechanisms leading to hyponatremia in patients with AMI are complex. The nonosmotic release of vasopressin may be precipitated by acute development of heart failure and response to pain, nausea, and stress and may play a role in the development

![Figure 2. Kaplan–Meier curve for crude cumulative 3-year mortality according to hyponatremia based on (A) baseline, (B) nadir, and (C) discharge sodium level.](image)

**Table 2**

Unadjusted and adjusted Cox proportional hazards model for mortality according to baseline, nadir, and discharge sodium analyzed as categorical and continuous variables.

| Effect of baseline sodium level, mEq/L | N  | Death, % | HR (95% CI) | P     | HR (95% CI) | P     |
|---------------------------------------|----|----------|-------------|-------|-------------|-------|
|                                       |    |          | Unadjusted  |       | Adjusted    |       |
| Continuous (per 1 mEq/L decrease)     |    |          |             |       |             |       |
| Sodium ≥135 mEq/L                     | 1554| 144 (9.3%)| 1 (Reference)|       | 1.02 (0.98–1.06)| .412  |
| Sodium < 135 mEq/L                    | 309 | 47 (15.2%)| 1.76 (1.27–2.45)| .001 | 1.10 (0.75–1.60)| .634  |
| Categorical variable                  |    |          |             |       |             |       |
| Sodium ≥135 mEq/L                     | 1345| 105 (7.8%)| 1 (Reference)|       | 1.04 (1.00–1.08)| .074  |
| Sodium < 135 mEq/L                    | 518 | 86 (16.6%)| 2.33 (1.75–3.10)| <.001 | 1.34 (0.96–1.88)| .068  |
| Effect of nadir sodium level, mEq/L   |    |          |             |       |             |       |
| Continuous (per 1 mEq/L decrease)     |    |          |             |       |             |       |
| Sodium ≥135 mEq/L                     | 1345| 105 (7.8%)| 1 (Reference)|       | 1.06 (1.01–1.11)| .026  |
| Sodium < 135 mEq/L                    | 518 | 86 (16.6%)| 2.33 (1.75–3.10)| <.001 | 1.34 (0.96–1.88)| .068  |
| Categorical variable                  |    |          |             |       |             |       |
| Sodium ≥135 mEq/L                     | 1716| 162 (9.4%)| 1 (Reference)|       | 1.71 (1.06–2.75)| .028  |
| Sodium < 135 mEq/L                    | 147 | 29 (19.7%)| 2.40 (1.61–3.56)| <.001 | 1.71 (1.06–2.75)| .028  |

BMI = body mass index, CI = confidential interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio, LVEF = left ventricular ejection fraction, NSTEMI = non-ST-segment elevated myocardial infarction, STEMI = ST-segment elevated myocardial infarction.

*The following baseline characteristics were considered in the multivariate analysis: age, gender, BMI (≥ 25 kg/m²), comorbidities (hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, and smoking status), Killip class, LVEF (≥ 45%), diagnosis (STEMI vs NSTEMI), eGFR on admission (< 60 mL/min/1.73 m²), reperfusion strategies (angioplasty and thrombolysis), and medical treatments during hospitalization.*
of hyponatremia.\[17,24,25\] Elevated vasopressin increases water permeability in the renal collecting duct through the insertion of aquaporin-2 channels into the collecting duct cell membrane. Neurohormonal activation also leads to the development of hyponatremia in AMI. In patients with AMI, marked stimulation of the sympathetic nervous system and renin–angiotensin–aldosterone system leads to vasoconstriction.\[11,26\] The subsequent decrease in glomerular filtration rate and delivery of tubular fluid to the dilution segment of nephrons further contributes to retention of free water.\[17,23\] Therefore, hyponatremia in AMI may reflect the severity of the disease, including left ventricular dysfunction, hemodynamic alteration, and extent of neurohormonal activation. The association between hyponatremia and increased mortality among patients with AMI is explained, in part, by these factors that characterize hyponatremia. Importantly, serum sodium level can be changed during hospitalization depending on alteration of these predisposing factors. Our study supports this assumption, showing that the incidence of hyponatremia varied by time during the hospitalization period.

Goldberg et al\[5,6\] suggested that hyponatremia on admission or shortly thereafter is an independent predictor of short-term and long-term mortality in STEMI. However, primary angioplasty was performed in <30% of patients in these studies. Klopotowski et al\[8\] investigated the influence of hyponatremia on in-hospital deaths in 1858 patients with STEMI treated using primary angioplasty. They observed that hyponatremia on admission was an independent predictor of in-hospital death only in patients with an LVEF of ≥40% or eGFR ≥60 mL/min/1.73 m². Lazzeri et al\[29\] recently showed that in STEMI patients, hyponatremia should be considered a marker of disease severity, rather than an independent predictor of short-term and long-term mortality. The conflicting results described above are mainly attributed to differences in the management of AMI between studies, particularly with respect to primary intervention and evidence-based medical treatment. Advances in these therapeutic approaches prevent progression of heart failure and attenuate neurohormonal activation and have contributed to the improved survival outcomes of patients with AMI in recent decade.\[15\] The impact of hyponatremia on clinical outcomes should therefore be reinterpreted in this era of primary intervention.

Our results are in agreement with those of Lazzeri et al\[29\] regarding the impact of baseline serum sodium level on long-term mortality. Furthermore, our study provides additional information on the association between serum sodium levels at various time points and long-term mortality. Our findings improve the understanding of the prognostic impact of hyponatremia during hospitalization for AMI and enable risk stratification in survivors of the acute episode.

A recent case–control study showed that hyponatremia is an independent predictor of in hospital mortality, and hyponatremia per se is likely to contribute to excess mortality between cases and constantly normonatremic controls (serum sodium level 135–145 mEq/L).\[30\] Moreover, Qureshi et al\[31\] showed that a corrected serum sodium level >134 mEq/L at discharge had no effect on the short-term mortality of patients with AMI but had a beneficial effect on long-term mortality compared with persistent hyponatremia. Interestingly, our finding also showed that, among the various time points, hyponatremia at discharge had the strongest association with long-term mortality in patients with AMI. Therefore, on the basis of this and previous studies, correction of hyponatremia during hospitalization might be necessary to reduce long-term mortality, even in mild hyponatremia patients.

The present study has several limitations. First, this is a retrospective, single-center, observation study. Second, although we adjusted for multiple confounding factors, we cannot exclude the possibility of residual confounding factors as a result of the presence of an unmeasured confounder or measurement errors in the included factor. In addition, serum sodium measurements are performed more frequently in patients with more severe symptoms, and this may increase the probability of detecting hyponatremia. Finally, because of the methodological limitations of retrospective analysis, we cannot provide information regarding neurohormonal activation which might explain the association hyponatremia and adverse outcomes, serum creatinine levels at various time points, and the identification of acute kidney injury at admission. However, previous studies have reported that initial renal dysfunction on admission can predict the short-term and long-term mortality of patients with AMI.\[32,33\] Therefore, using the eGFR to determine the renal dysfunction at baseline might be valuable for evaluating the relationship between the presence of hyponatremia and long-term mortality in our study. Nevertheless, despite the limitations listed above, our study has several notable strengths worth mentioning. First, we evaluated the association between hyponatremia at various time points during hospitalization and long-term mortality in patients with AMI. Second, this study included a large number of patients and provided long-term follow-up data over a mean period 3.7 years. In conclusion, we found that the serum sodium level and incidence of hyponatremia varied during hospitalization according to time of measurement and that the association between sodium level and long-term mortality also differed at various time points during hospitalization. The discharge sodium level, among the various time points, appears to be best predictor of long-term mortality in survivors of AMI.
AMI. Further prospective studies are needed to determine whether hyponatremia is causally linked to long-term mortality and to confirm whether correction of hyponatremia could affect the clinical outcomes in patients with AMI. Moreover, given the deleterious effects of rapid correction of hyponatremia at lower sodium levels, further studies are required to evaluate the strategy and optimal agents of correction of hyponatremia.

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