Author's response to reviews

Title: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: a prospective observational study

Authors:

Seung Seok Han (hansway80@gmail.com)
Dong Ki Kim (dkkim73@gmail.com)
Yon Su Kim (yonsukim@snu.ac.kr)
Jin Suk Han (jshan@snu.ac.kr)
Kwon Wook Joo (junephro@snu.ac.kr)

Version: 2  Date: 4 December 2015

Author's response to reviews: see over
Reviewer's report

Title: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: a prospective observational study

Version: 1  Date: 18 September 2015

Reviewer: Kianoush Kashani

Reviewer's report:

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
  - The article needs significant language improvement. It needs to be reviewed by someone whose speak English as the mother tongue.

# Example: Authors say: “The distributions of AKI causes were different among sodium groups. Hyponatremia groups had higher scores on the Charlson Comorbidity Index than the normonatremia group.” CCI is only an indicator of risk for AKI, not the cause.

  We apologize for the nonfluent text. However, the two sentences that the reviewer commented on addressed separate issues. The former sentence indicated that the causes of AKI (i.e., sepsis, surgery, nephrotoxin, and others) differed among the hyponatremia, normonatremia, and hypernatremia groups. The latter sentence indicated that the CCI value in the hyponatremia group was higher than in the normonatremia group, and we did not use CCI as a cause. All differences are described based on Table 1 (baseline characteristics). Nevertheless, we totally agree that the English text should be improved. Accordingly, we have further revised the manuscript with the assistance of a professional English editing service.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term,
which the author can be trusted to correct)

o Authors corrected sodium for glucose. This formula may not be correct when glucose is more than 400. They need to present median and IQR of glucose level.

    We agree with the reviewer’s comments. The median (IQR) of the glucose level was 152 mg/dL (115 to 218 mg/dL). The histogram of glucose levels is shown below:

Figure. Histogram of glucose level.

Among the study patients, 11 (1.9%) had glucose levels more than 400 mg/dL. Most patients had glucose levels less than 400 mg/dL. According to a previous study of 6 healthy individuals (Hillier TA et al. Am J Med 1999;106:399-403), the correction factor (standard: 1.6) may be higher for glucose levels >400 mg/dL. Most of our patients had glucose levels less than 400 mg/dL, and we could not calculate the modified correction factor because of the observational design. We have reported the glucose levels and discussed the limitation of our correction in the revised manuscript. We would like to thank the reviewer for the helpful
Authors mentioned they used hypo or hypertonic solutions to correct sodium during CRRT. They need to report how much of each solution was employed in each subgroup and total.

As the reviewer recommended, we retrieved the data on the hypo or hypertonic solutions used. Treatment with hypertonic saline was used in 8 patients, of whom 7 had moderate to severe hyponatremia and 1 had mild hyponatremia. Hypotonic saline was used in 29 patients, of whom 13 had mild hypernatremia and 16 had moderate to severe hypernatremia. The uses of hypotonic saline in the normonatremic patients (n=78) were attributable to the infusion of nutrients (e.g., mixtures with multivitamins). We have added the use of each solution in the revised manuscript.

We appreciate the reviewer’s comments, which improved the reliability of the study.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

What is sodium score? How they come up with this score? This is wrong assumption that this formula corrects sodium for the severity of illness. Have they validated it? In addition this assumes there is a linear relationship between the severity of acute disease and sodium level, which is not proven by their data.

We totally agree with the reviewer’s comments. Initially, we thought the sodium correction (total APACHE score minus the allocated sodium points) might be needed because some hyponatremia studies used a similar method (Intensive Care Med 2010;36:304-311). However, we agree with the comments, since the sodium-corrected APACHE scores are not validated. We have deleted the description for the sodium-corrected APACHE score and have
used only the total APACHE score throughout the revised manuscript. Thank the reviewer for the helpful comments.

**Level of interest:** An article of limited interest  
**Quality of written English:** Not suitable for publication unless extensively edited  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:** I declare that I have no competing interests
Reviewer's report

Title: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: a prospective observational study

Version: 1 Date: 21 September 2015

Reviewer: Sagar U. Nigwekar

Reviewer's report:

Authors address an important and well-defined question regarding association between dysnatremia and its correction with short term mortality in critically ill population undergoing CRRT. The methods are appropriate and well described for this observational study. The findings of lack of association between correction of dysnatremia and mortality are rather provocative since clinical practice at present is based on the assumption that rate of sodium correction is an important predictor of outcomes.

Major compulsory revision:
None

Minor essential revision:

My only concern is as follows: Most robust data regarding rate of sodium correction and outcomes are for neurological outcomes and in that regard authors should either report cause specific mortality for neurological conditions and/or incidence of neurological events. If these data are not available then authors should acknowledge this as a limitation.

We would like to thank the reviewer for a good suggestion. We totally agree with the reviewer’s comments that the correction rate for both hyponatremia and hypernatremia is essential in clinical practice (Semin Nephrol 2009;29:282-299). In addition, we acknowledge that the issue of sodium correction might be inconclusive because we could not consider its rate. We could not retrieve the neurologic outcomes, because most patients received
mechanical ventilation at the time CRRT commenced. We have described the limitation in the revised version of the manuscript.

We would like to thank the reviewer for the helpful comments.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:** None
Reviewer's report

Title: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: a prospective observational study

Version: 1 Date: 4 September 2015

Reviewer: Arthur Greenberg

Reviewer's report:

The authors attempted to assess the influence of hyponatremia and hypernatremia on 30 day mortality of patients with AKI who required continuous renal replacement therapy. In addition, they examined the effect of correction of dysnatremia on mortality in this same population.

The adverse effect of dysnatremia on mortality is well documented in numerous situations. This manuscript adds another population. Data on effect of correction of dysnatremias in large populations are scarce. The data provided by the authors in this population are an important addition to the literature.

Major Compulsory /Revisions:

1. How the population enrolled was acquired in incompletely specified. Were the cases consecutively ascertained? What percentage of patients approached declined enrollment. The authors should provide a CONSORT diagram detailing patient flow as a supplemental figure.

We agree with the reviewer. During the study period, a total of 8,829 patients admitted to the ICU. Among them, 1,110 patients received CRRT and 669 patients agreed with the study participation. Finally, 569 patients were analyzed for the study. The present study design was an observational cohort study, and thus we have provided the STROBE checklist and CONSORT flow diagram (as below) in the revised manuscript.
2. The authors mention correction for comorbidities, but provide details only on the modification to APACHE scores. If they performed a multivariate correction (table 2), they need to provide details on their model.

We adjusted all the covariates in the multivariate models, including age, sex, enrollment year, weight, cause of acute kidney injury, dialysis dose, need for mechanical ventilation, use of vasoactive drugs, chronic kidney disease, Charlson Comorbidity Index, APACHE II score, creatinine, albumin, urine output, fluid balance, and onset of dysnatremia. As per the reviewer’s recommendation, we have described the adjusted factors in the method section and tables of the revised manuscript.
3. The authors repeatedly state that the available prior studies do not show a survival benefit for correction of hyponatremia. No study performed to date was designed or powered to show a mortality effect. The studies have all used sodium concentration correction as the metric for benefit. The comments on the EVEREST trial in the discussion need either to be deleted or reworked. The objective of this trial had nothing to do with dysnatremia. It was designed only to assess the effect of treatment with a vasopressin receptor antagonist on outcome of acute decompensated CHF. Only 7% of patients were dysnatremic. A secondary analysis of the hyponatremic patients suggests benefit of improved hyponatremia, (Hauptman PJ. J Card Fail 2013;19:390), but this study is merely hypothesis generating.

We totally agree with the reviewer’s comments. There are no RCTs studying survival with dysnatremia correction. We acknowledge the purpose of the EVEREST trial was not the dysnatremia correction. Accordingly, we have deleted the comments on the EVEREST trial in the revised manuscript.

4. Patients with AKI receiving CRRT are very sick. Numerous trials in patients with AKI, ESRD, sepsis in the ICU, and other highly complex illness have failed to show a mortality benefit of a single simple maneuver, e.g., increased dialysis dose, goal-directed fluid management, glucocorticoids, anti-thrombin 3. The authors should emphasize in the discussion the difficulty of showing improvement of therapeutic maneuvers in patients with multi-system illness. This is particularly important in this purely observational study.

The reviewer’s comments are appreciated. Initially, we tried to address the difficulty in determining survival outcomes under the strong influence of comorbidities. Recent data (Kidney Int 2015;88:167-177) also suggested the influence of comorbidities on the therapeutic benefit. In this regard, it was difficult to prove the therapeutic efficacy of sodium
correction in our population, although we tried to enroll a homogeneous group (i.e., CRRT) with a large sample size. We have further emphasized this issue in the limitation section of the revised manuscript.

Minor Essential Revisions:

5. Are figures 4E and 4F correctly labeled? They appear to show higher mortality in patients with hypernatremia at baseline whose sodium fell, i.e., corrected, at 24 or 72 hours. The text describes improved mortality with correction in this group.

   The figures are correct. These figures showed a large 95% CI range, and thus most changes (-15 mmol/L in Figure 4E [24 hours]; the entire range in Figure 4F [72 hours]) were not associated with either improved or worsened mortality. However, at least the adjusted mortality rate decreased in the range less than -15 mmol/L in Figure 4E. To aid in understanding, we have revised the result section in detail.

6. Suggested language changes:

   p4, line 6. substitute "adverse" for "worse"

      We have changed “worse” to “adverse”.

   p. 4, line 23 change to "how sodium levels predict mortality". "Predictability" is not a suitable term here.

      We have changed the sentence as per the reviewer’s comment.

   p. 12, line 12. meaning of "issues are waived" is unclear. Rewrite.

      We have re-written the sentence as follows:
“In addition to the correlation issue between dysnatremia and mortality”.

In addition, we have revised the manuscript with the assistance of a professional English proofreading English editing service.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:** Within the last 5 years, I have received consulting fees, research support, travel support, and served on a Speaker Bureau for Otsuka, the manufacturer of tolvaptan.
Reviewer's report

Title: Dysnatremia, its correction, and mortality in patients undergoing continuous renal replacement therapy: a prospective observational study

Version: 1 Date: 22 August 2015

Reviewer: Tae-Hyun Yoo

Reviewer's report:

The manuscript by Han et al. examines the impact of dysnatremia on all-cause mortality in patients undergoing continuous renal replacement therapy (CRRT). Patients were divided on the basis of serum sodium concentrations measured at baseline, 24 hours, and 72 hours after application of CRRT. Subsequently, 30-day mortality was analyzed by classifying patients as moderate to severe or mild hyponatremia/hypernatremia, while the normonatremia group was used as reference. This study demonstrated the well-known associations between dysnatremia and mortality in CRRT patients. The present study is interesting but has some issues to be addressed:

1. Confounding factors including for multivariate analysis should be mentioned in the manuscript and table.

   We adjusted all the covariates in the multivariate models. As per the reviewer’s recommendation, we have described the adjusted factors in the revised manuscript and tables.

2. During the follow up, does any difference in mortality rate according to unchanged sodium groups? Rather than evaluating the impact of changes in sodium levels, author can analyze the mortality rate in three groups such as hypo-hypo, normo-normo, hyper-hyperNa groups. If possible, readers can understand the impact of sodium on the mortality rate in this population.
We would like to thank the reviewer for a good suggestion. Actually, our previous analyses included all of the hypo-hypo, normo-normo, and hyper-hyper groups (Table 3, Figure 4, and Additional file 1). When we compared the mortality rates between the groups after adjusting covariates, change or non-change was not associated with mortality risk. When we compared the mortality rates only within three groups (i.e., hypo-hypo, normo-normo, and hyper-hyper groups), the results were as follows:

Table. Adjusted odd ratios of mortality among the sodium groups such as normonatremia-to-normonatremia, hyponatremia-to-hyponatremia, and hypernatremia-to-hypernatremia.

<table>
<thead>
<tr>
<th>Group</th>
<th>24 hours</th>
<th></th>
<th>72 hours</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>n</td>
</tr>
<tr>
<td>Normo to normo</td>
<td>181</td>
<td>1 (Reference)</td>
<td>128</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Hypo to hypo</td>
<td>105</td>
<td>2.09 (0.841–5.172)</td>
<td>0.113</td>
<td>77</td>
</tr>
<tr>
<td>Hyper to hyper</td>
<td>18</td>
<td>1.96 (0.557–6.886)</td>
<td>0.295</td>
<td>8</td>
</tr>
</tbody>
</table>

The normo- to normonatremia groups were included at later normonatremia groups (i.e., 24-hour normonatremia or 72-hour normonatremia). The hypo- to hyponatremia and hyper- to hypernatremia groups were also included at later hyponatremia and hypernatremia group, respectively. As shown in Table 3, we determined that later sodium levels did not predict mortality risk. As per the reviewer’s recommendation, we have performed a subgroup analysis (focusing on non-change groups) and have described this in the result section and Additional file 2 of the revised manuscript.

3. Please describe mortality rate according to sodium groups.
As per the reviewer’s recommendation, we have described the mortality rate for each sodium group in the revised manuscript.

4. Were all the patients positive I/O balance?

We collected data on fluid balance, indicating total input minus total output, as described in the method section. The mean values (Table 1) were all positive, but the standard deviations were large. This indicates the range of I/O was broad. At 24 hours, 161 patients had negative I/O; at 72 hours, 265 patients had negative I/O.

Referentially, we also assessed the change in body weight to determine the balance between input and output, as follows:

Table. Change of body weights after 24 and 72 hours.

<table>
<thead>
<tr>
<th>Group</th>
<th>24 hours (kg)</th>
<th>P*</th>
<th>72 hours (kg)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe hyponatremia</td>
<td>0.3 ± 2.15</td>
<td>0.535</td>
<td>-0.8 ± 3.21</td>
<td>0.153</td>
</tr>
<tr>
<td>Mild hyponatremia</td>
<td>0.6 ± 3.55</td>
<td>0.154</td>
<td>-1.2 ± 2.77</td>
<td>0.614</td>
</tr>
<tr>
<td>Normonatremia</td>
<td>0.1 ± 2.50</td>
<td>–</td>
<td>-1.4 ± 2.54</td>
<td>–</td>
</tr>
<tr>
<td>Mild hypernatremia</td>
<td>0.0 ± 3.23</td>
<td>0.870</td>
<td>-0.9 ± 3.93</td>
<td>0.439</td>
</tr>
<tr>
<td>Moderate to severe hypernatremia</td>
<td>1.1 ± 1.93</td>
<td>0.010</td>
<td>-0.2 ± 2.67</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*Difference is calculated based on the normonatremia.

The changes in weight did not differ between groups except for the moderate to severe hypernatremia group. The data showed the same trend for I/O (i.e., fluid balance). Accordingly, we believe that the data on fluid balance were correct.
We would like to thank the reviewer for the helpful comments.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** 'I declare that I have no competing interests'