PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between intensive care unit-acquired hypernatraemia and mortality in critically ill patients with cerebrovascular diseases: a single centre cohort study in Japan
AUTHORS	Imaizumi, Takahiro; Nakatochi, Masahiro; Fujita, Yoshiro; Nomura, Rie; Watanabe, Kenshi; Maekawa, Michitaka; Yamakawa, Taishi; Katsuno, Takayuki; Maruyama, Shoichi

VERSION 1 - REVIEW

REVIEWER	Marjolein van IJzendoorn Medical Center Leeuwarden, the Netherlands
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	Firstly: I think this manuscript addresses an important issue, namely: in ICU-patients with a neurological reason for admission elevated serum sodium levels are accepted (although literature on the benefit of increasing serum sodium concentration is scarce; the actual recommendation seems to be the avoidance of hyponatremia), but on the other hand there is a lot of evidence that (ICU-acquired) hypernatremia is harmful. In that light this study is useful in answering the question if 'permissive hypernatremia' in neurological ICU-patients outweigh the harmful effects of hypernatremia itself. The objective, study population, data collection and statistics are well described. Also this study supports previous literature about IAH being harmful. Another positive point is that the authors do not claim (to prove) more than they actually do in the manuscript. However, I have a major concern about the manuscript. Although the title of the manuscript is 'The association between IAH and mortality in critically ill patients with CVD (...)' only a rather small part of the manuscript focuses on IAH in patients with CVD. Indeed the conclusions of the manuscript fit the title, but for these conclusions data about patients with other reasons for admission could be left out. I would suggest to focus more on patients admitted with CVD (or change the title of the manuscript). My main questions are: * What are the characteristics of patients with CVD that do and do not develop IAH? (In fact table 3, but variables computed separately for patients that do and do not develop IAH) * What was the median duration of IAH? * How was kidney function in patients with CVD? * Were there patients with CVD on renal replacement therapy? * Were data collected about the presence of cerebral edema? / Was intracranial pressure measured? When yes, were differences observed in patients with or without cerebral edema / differences in ICP between patients that did and did not develop IAH?

	I also have some minor concerns:
	1) Literature on the benefits of actively raising serum sodium concentration is scarce, especially for patients with CVD. In fact most authors / guidelines recommend avoiding hyponatremia instead of inducing hypernatremia. Even the article by Qureshi et al. that is mentioned in the introduction only found lowering of ICP (without data about mortality) in patients with traumatic brain injury and in patients after surgery, not in patients with CVD. In the discussion of the manuscript also is mentioned that in the institution where the study was conducted an osmotic diuretic was administered to patients with CVD. Based on the literature the question arises if this is treatment is recommendable. I would suggest to address the doubts about persuading hypernatremia (instead of avoiding hyponatremia), especially because this study again showed the harmful effects of IAH.
	2) I would recommend an 'interpretation guideline'/legend for the cubic spline figures, to explain the different lines

REVIEWER	JL Vincent Dept of Intensive Care Erasme university Hospital Université Libre de Bruxelles Brussels, Belgium
REVIEW RETURNED	11-Apr-2017

GENERAL COMMENTS	The authors describe the relation between hypernatremia and outcome in a series of patients with cerebrovascular disease. The paper suffers from a number of limitations: 1. This relation is well known in neurological patients like in others (as discussed by the authors); 2. It is a single-center, retrospective study; 3. The population is quite heterogeneous; the results in an isolated population of patients with cerebral edema may be of some interest, but should optimally be prospective and multicentric. 4. The proposed threshold value is not very convincing: the more severe the hypernatremia, the worse the outcome.

REVIEWER	Edson Zangiacomi Martinez University of São Paulo, Brazil
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	This is an interesting article about how the intensive care unit-acquired hypernatraemia can be an important predictor for mortality in critically ill patients with cerebrovascular diseases. Considering that my expertise is in medical statistics, I wish point out some considerations: (a) Page 2, line 36. I think the correct expression is "...were associated with time to death...", instead of "mortality". (b) Page 2, line 52. The authors inform that restricted cubic splines were used to study the shape of the association between maximum serum sodium concentration and the risk of mortality. However, in Page 8, line 43, it is informed that cubic polynomials models were used in this task. Please, inform correctly the model used in this analysis. (c) The authors should provide more details about the Figures

| | showed in Page 26. It is unclear as the readers can interpret this figures. There are not explanations about the dashed and full lines.
 (d) Page 6, line 45, "biochemical parameters" => "biochemical variables" (see Altman, D. G., & Bland, J. M. (1999). Statistics notes: Variables and parameters. BMJ, 318(7199)1667).
 (e) Table 1. There are an unknown symbol after "body temperature". |

VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer 1

Major revisions:
#1
Although the title of the manuscript is 'The association between IAH and mortality in critically ill patients with CVD (...)' only a rather small part of the manuscript focuses on IAH in patients with CVD. Indeed the conclusions of the manuscript fit the title, but for these conclusions data about patients with other reasons for admission could be left out. I would suggest to focus more on patients admitted with CVD (or change the title of the manuscript).

Response:
Thank you for your constructive comment. Since this study is also a summary of research for sodium disturbance in all critically ill patients who were admitted to ICU, we described the characteristics of all patients. However, the patients with CVD were of more interest as you mentioned, we described the variables which we used in the multivariate analysis for all patients in Table 1. We described the detailed baseline characteristics of patients with CVD in Table 3.

#2
What are the characteristics of patients with CVD that do and do not develop IAH? (In fact table 3, but variables computed separately for patients that do and do not develop IAH). How was kidney function in patients with CVD? Were there patients with CVD on renal replacement therapy?

Response:
We appreciate the reviewer's valuable suggestions. In response to the comments, we described the detailed baseline characteristics of patients with CVD in Table 3. As requested, we described each variable separately for patients with and without IAH. We also revised the result section to describe the difference in the clinical characteristics of CVD patients with IAH and those without IAH as following; "Among those with CVD, 33 patients had IAH. Patients with IAH had significantly lower in GCS scores, and significantly higher in APACHE-II and modified Rankin scale scores than patients without IAH. Moreover, a significantly higher proportion of patients with IAH required mechanical ventilation. The incidence of AKI was not significantly higher in the patients with IAH. Twenty-eight patients among those with CVD died within 28 days. ICU and in-hospital mortality rates were higher and the length of ICU stay was longer for patients with IAH." (Page 14, line 11) We also made some minor revisions as following text; "The clinical characteristics of patients with CVD are shown in Table 3. In this study, there were 93 patients had a subarachnoid haemorrhage, 159 had a cerebral haemorrhage, and 94 had suffered an ischemic stroke" (Page 14, line 6)
#3
What was the median duration of IAH?

Response:
Thank you for your comment. We think this is a very important point. The median duration of IAH was 4 [3-8] days in total and 3 [2-8] days for patients with CVD. We revised the manuscript as following;
"The median duration of IAH was 4 [3-8] days in total and 3 [2-8] days for patients with CVD." (Page

9, line 27)

#4
Were data collected about the presence of cerebral oedema? / Was intracranial pressure measured? When yes, were differences observed in patients with or without cerebral oedema / differences in ICP between patients that did and did not develop IAH?

Response:
We wish to express our appreciation to the reviewers for their insightful comments on our paper. The comments have helped us significantly improve the paper. As a general clinical practice in Japan, ICP measurement is not routinely performed when managing critically ill patients with CVD. Nevertheless, osmotic diuretics such as glycerol are frequently administered for such patients. This might have contributed to hypernatraemia in some patients, leading to a poor prognosis. On the other hand, a previous report (Randall et al. NEJM 2012) suggested that the measurement of intracranial pressure may not always give a good prognosis. However, we do not agree on the use of osmotic diuretics without assessing intracranial pressure. So, we added the following sentence in the limitation section; "since ICP measurement was not routinely performed, this study was unable to focus on patients with cerebral oedema. Nevertheless, osmotic diuretics such as glycerol are frequently administered in routine clinical practice in Japan. This might have contributed to hypernatraemia in some patients, leading to a poor prognosis." (Page 19, line 18)

Minor revisions:
#5
Literature on the benefits of actively raising serum sodium concentration is scarce, especially for patients with CVD. In fact, most authors guidelines recommend avoiding hyponatremia instead of inducing hypernatremia. Even the article by Qureshi et al. that is mentioned in the introduction only found lowering of ICP (without data about mortality) in patients with traumatic brain injury and in patients after surgery, not in patients with CVD. In the discussion of the manuscript also is mentioned that in the institution where the study was conducted an osmotic diuretic was administered to patients with CVD. Based on the literature the question arises if this is treatment is recommendable. I would suggest that you address the doubts about persuading hypernatremia (instead of avoiding hyponatremia), especially because this study again showed the harmful effects of IAH.

Response:
We wish to express our deep appreciation to the reviewer for his insightful comment on this point. As the reviewer pointed out, there is little evidence as to the benefits of positively raising serum sodium levels or the active use of osmotic diuretics, especially for patients with CVD. Nevertheless, in Japan, intravenous administration of hypertonic glycerol is a frequent choice for acute stroke without assessing intracranial pressure. I think such clinical practice are not always be justified. So, we added the following text in the discussion section, and also two references in reference section appropriately; Evidence on the benefits of actively raising the serum sodium concentration and the active use of osmotic diuretics is lacking, especially for patients with CVD. Patients with lower GCS scores, or those with clinical evidence of trans tentorial herniation might be considered for intracranial pressure (ICP) monitoring and treatment according to the guidelines for the management of spontaneous intracranial haemorrhage (Stroke 2015, AHA). Methods of treating elevated ICP are generally borrowed from traumatic brain injury guidelines as well. Osmotic diuretics or hypertonic saline may be used to treat acute elevations of ICP; hypertonic saline may be the more effective agent. However, this recommendation is effective only if ICP is monitored. Despite this, intravenous administration of hypertonic glycerol is commonly used in the treatment of acute stroke in Japan, often without concomitant ICP measurement (Cerebrovasc Dis 2013;35:419–429). (Page 17, line 48)

#6
I would recommend an 'interpretation guideline' legend for the cubic spline figures, to explain the different lines

Response:
We appreciate the reviewer's comment on this point. In accordance with the reviewer's comment, we have changed the legend of Figure 3 as following:
"Figure 3. Association between maximum and minimum sodium concentrations and mortality (adjusted odds ratio and 95% confidence intervals) by restricted cubic spline model (3 knots) in patients with cerebrovascular diseases. The dashed lines represent the 95% confidence intervals for the spline model.
A. Maximum sodium concentration and 28-day mortality. (Reference: 144 mEq/L) The curve's nadir was between 141 and 146 mEq/L.
B. Minimum sodium concentration and 28-day mortality. (Reference: 141 mEq/L) The spline curve was not significantly associated with mortality."
Reviewer: 2

The reviewer pointed out several limitations.
#1. This relation is well known in neurological patients like in others (as discussed by the authors);
#2. It is a single-center, retrospective study;
#3. The population is quite heterogeneous; the results in an isolated population of patients with cerebral edema may be of some interest, but should optimally be prospective and multicentric.
#4. The proposed threshold value is not very convincing: the more severe the hypernatremia, the worse the outcome.

Response:
Thank you for your comment. We would like to answer point by point.
#1 We have already known this association in other neurologic conditions. This study focused on the patients with cerebrovascular diseases.

#2 This was a single-centre study as the reviewer pointed out. There are concerns that this limitation might generalize biased practice patterns like usage of osmotic diuretics or measurement of intracranial pressure. So, we added the following sentence; "Third, a single-centre study may be biased by local practice patterns, such as the use of osmotic diuretics or measurement of ICP." (Page 19, line 15)

#3 As the reviewer pointed out, the results in an isolated population of patients with cerebral oedema are of some interest. It is a very important point. We added the comment in the discussion section. (Same as the response of #4, reviewer 1)

#4 The restricted cubic spline analysis showed not only the threshold of the maximum sodium concentration but also the fact that the more severe the hypernatremia, the worse the outcome. We agree on this point, and have added the following text: "Second, using RCS analysis, a dose-response association between serum sodium concentration and mortality risk was observed, and the optimal serum sodium target concentration for patients with CVD was determined to be ≤ 146 mEq/L." (Page 17, line 11)

Reviewer: 3

(a) Page 2, line 36. I think the correct expression is "...were associated with time to death...", instead

of "mortality".

(b) Page 2, line 52. The authors inform that restricted cubic splines were used to study the shape of the association between maximum serum sodium concentration and the risk of mortality. However, in Page 8, line 43, it is informed that cubic polynomials models were used in this task. Please, inform correctly the model used in this analysis.

(c) The authors should provide more details about the Figures showed in Page 26. It is unclear as the readers can interpret these figures. There are not explanations about the dashed and full lines.

(d) Page 6, line 45, "biochemical parameters" => "biochemical variables" (see Altman, D. G., & Bland, J. M. (1999). Statistics notes: Variables and parameters. BMJ, 318(7199)1667).

(e) Table 1. There is an unknown symbol after "body temperature".

Response:
We are grateful for your constructive comment for the statistical analysis. We revised the manuscript as the reviewer pointed out.
(a) We revised the sentence as the reviewer pointed out. (Page 2, line 36)

(b) We revised the concise explanation of restricted cubic splines in the methodology section as following; "In the RCS, the non-linear association between predictor and outcome was expressed as a spline curve combined cubic polynomials and linear terms." (Page 8, line 43)

(c) We revised the figure legend. (Same as the response of #6, reviewer 1)

(d) We revised the sentence as the reviewer pointed out. (Page 6, line 45)

(e) We converted the symbol "℃" to Unicode.

VERSION 2 – REVIEW

REVIEWER	Edson Zangiacomi Martinez University of São Paulo (USP), Brazil
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	Accept.