Author's response to reviews

Title: Undercorrection of hypernatremia is frequent and associated to mortality.

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Author's response to reviews: see over
Marseille, 15th January 2014

Dear Editor-in-Chief,

We thank you for having considered our original article entitled "Undercorrection of hypernatremia is frequent and associated to mortality." for publication in BMC Nephrology.
Please find below the answers to reviewers' concerns and the modified manuscript. We hope that the changes made will fulfill the editorial board and the reviewer's questions.

Sincerely,
Stanislas Bataille, MD
Answers to Editorial Requests:

General Remarks.
The authors have made some modifications in the re-submitted manuscript which have improved the study. Enhanced formatting, improved clarity of the text and the tables has improved the readability of the paper. The inclusion of the univariate and multivariate analysis has also been helpful but these I feel require further consideration. However, notwithstanding these improvements, this reviewer continues to have residual concerns regarding the internal validity of the study and the final take home message.

In essence, this is a subgroup analysis of all patients with hypernatremia admitted to a regional emergency centre and highlights heterogeneity in management and outcomes. In general the outcomes are similar to those of recently published studies which the authors cite. I have residual concerns regarding the robustness of the analysis, the final conclusions with respect to the rate of sodium correction and external validity. I would suggest that particular attention be given to these.

1. Limited sample size
The analysis is limited to 85 patients who are old and frail with serum sodium concentrations of > 150 mmol/L. Consequently the analysis lacks power to make a clinically meaningful conclusion regarding mortality risk factors and the contribution of the speed of correction of serum sodium to mortality.

We agree that number of patient in the analysis is limited and thus our study probably lacks of power to show all mortality risk factors. Nevertheless, within all studies performed in emergency department (which are reported in Table 4 of our paper), our study is the second biggest study. Moreover, the biggest study, performed by Arampatzis et al. which includes 400 hypernatremic patients is only a descriptive study in which mortality risk factors haven't been performed.

The small size of the cohort has already been highlighted in the discussion paragraph: "The 85 cases analyzed represent a relatively small cohort and there were numerous confounding factors such as loss to follow-up, associated comorbidities, and associated acute illness. The small cohort size also probably explains why the relationship between
hypernatremia and death did not reach statistical significance. Moreover, our monocentric study might reflect local practices and a local effect."

2. **Univariate and Multivariable analysis**

   Serum sodium was not significantly associated with mortality in the univariate analysis, most certainly due to small sample size. It appears that serum sodium was then not included in the multivariate model as it was correlated with another explanatory variable. From my reading of the analyses, the variable no natremia improvement (yes vs no) was included in the final model and its significance increased from $P=0.02$ to $P<0.001$. In other words the final model did not adjust for baseline serum sodium on admission to ER. I suspect this is why the no natremia improvement variable is so significant despite the small sample size. I also note that the rate of correction of serum sodium was not significant in the univariate model ($p=0.1$).

   We understand this concern and provide a new multivariate model including natremia at admission. Final results are identical to previous paper.

3. **Missing Data**

   Perfusion speed of correction was missing in 74% of patients as highlighted by the authors on page 12.

   Our Emergency Department is the biggest ED of the city. A high number of patients is admitted in the ED each day. Thus, in 74% of patients, perfusion speed of fluid was not reported in the medical files.

   We feel this is an important result because it highlights every day practices and the lack of precision in medical prescriptions and might explain the slow correction speed of natremia in hypernatremic patients.

   We also agree this is a concern. Since this study, our practices have been worked out to improve this point and modified the discussion:

   "We could not determine whether insufficient correction of hypernatremia was due to a low speed of perfusion because perfusion speed was missing in 74% of the cohort. This high percentage of missing data might reflect the lack of precision of medical prescriptions or the lack of transcription of the nurse on the medical file."
4. The conclusions are overstated. The lack of natremia improvement is not the same as a slow correction speed. Why wasn't the mean speed of correction included in the final model if the authors want to make a robust statement regarding the correction speed?

In the first version of the paper, statistical analysis were performed with the mean speed of correction but not the lack of natremia improvement and was statistically significant. However, confidence interval was very large and confusing. For this reason, all statistical analysis were redone. To provide improved statistics with relevant and understandable results, we chose to separate correction speed in quartiles. The lower quartile did in fact match with the "no improvement" group. For this reason, we included the "no improvement" parameter instead of correction speed.

5. Redundancy
I am not sure that manuscript benefits from inclusion of Figure 1a, b and c

Figure 1 was included to better visualize our results. If the Editor, which is more experienced than us, prefers to remove the Figure, we of course agree. Thank you for your kind remark.

6. Additional suggestions
1. I would delete objective (2) on page 5 as it is already covered in objective (1).

We modified this point as requested:
"In this study, we: (1) report clinical characteristics, management, outcome and mortality risk factors of severely hypernatremic patients admitted to the ED."

2. There is duplication in the results section as the descriptive narrative duplicates the message in the Tables.

We shortened the results section as required.

3. Replace sequels with sequelae on page 12

Done.
4. The narrative description provided on page 8-9 appears excessive and appears to duplicate the findings presented in the Tables. The authors should consider either a brief text description where the Table itself is self-explanatory. A more focused narrative on the results and subsequent discussion would be beneficial.

We shortened this section as proposed.
Answers to the reviewers:

Reviewer 1:

*The authors adequately addressed all my comments.*

We thank Reviewer 1 for his review.

Reviewer 2:

Comments of Reviewer 2 are identical to those of Editor. We hope that answers made to Editor will fulfill the reviewer's request.