Author’s response to reviews

Title: Investigation and management of moderate to severe inpatient hyponatraemia in an Australian tertiary hospital

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James Mockridge, PhD
Editor
BMC Endocrine Disorders

Dear Dr Mockridge,

Subject: Submission of revised paper “Investigation and management of moderate to severe inpatient hyponatraemia in an Australian tertiary hospital.” (BEND-D-18-00291)
Thank you for your email dated Thursday 4th of October enclosing the reviewers’ comments. We have carefully reviewed the comments and have revised the manuscript accordingly. Our responses are given in a point by point manner below. Changes to our manuscript are highlighted in yellow.

We hope that the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

Dr Kathryn Berkman
Endocrinologist

A/Prof Warrick Inder
Endocrinologist

Response to Reviewer 1: (Henrik Falhammar)

Thank you for your review of our paper. We have answered each of your points below.

1. Background: Mostly the same references [1, 2] are used in the entire section. Maybe add 1 or 2 more?

Response: Thank you for the suggestion. We have now cited three additional references:

- Ball SG, Iqbal Z (ref 5 - page 5, paragraph 2)
- Thompson C, Hoon EJ (ref 6 - page 5, paragraph 2)
- Berardi R et al (ref 8 - page 5, paragraph 3)
2. How many admissions were there in total to the PA hospital during the studied period and what was the frequency of severe hyponatremia among them?

Response: Thank you for this recommendation. There were 9774 admissions over the study period. There were 152 patients with severe hyponatraemia identified, which represents 1.6% of admissions. This has now been added to under the results section (Page 8, Line 171).

3. Page 6, Line 40: Maybe add the initials of the three investigators here as well and not just in the contribution section.

Response: This has been amended to include the 3 reviewers’ initials (Page 6, line 137)

4. Page 9, Line 6: Why was the cut off 400 mOsm/kg chosen?

Response: This cut off was chosen arising from the work of Winzeler et al. (ref 11) who found this cut-off predicted response to fluid restriction. This is expanded upon in the Discussion and has now been clarified in the Background section. (page 6, line 121-122)

5. What different teams (general medicine, general surgery, cardiology, endocrinology, neurology, nephrology, oncology, psychiatry, ICU etc.) where the patients admitted under? If the numbers are not too small, were there any differences in investigations, diagnosis and management between the team?

Response: Thank you, we have clarified the admitting teams as follows: Surgical units (41 of 152 patients (27%), General medicine (38 patients (25%)); followed by Cardiology (16 patients (10.5%)), Nephrology (13 patients (8.6%)), Gastroenterology (13 patients (8.6%)) and Respiratory (7 patients (4.6%)). (Page 8, Results, Line 173-176)

Differences in investigations, diagnosis and management could not be compared between these groups because Medical, Renal or Endocrine consults for surgical or other sub-specialty medical units rendered these data difficult to interpret.

6. References: Some references, e.g., nr 12, 14 and 15 have et al. after the first authors while others don't. Is there a reason?

Response: Apologies for the formatting error. This has now been amended to reflect standard Vancouver style referencing. i.e. The first 6 authors name in full followed by et al.
7. Drug-induced hyponatremia is common. Recently it has been reported that different antidepressants, antiepileptic drugs and proton pump inhibitors have different association with hyponatremia resulting in hospitalization. The risk seemed to only occur the first three months after commencing the drugs. Could more details be given of the different drugs the patients with severe hyponatremia was using when being admitted and when these had been commenced?

Response: Thank you for this excellent suggestion. Unfortunately, we are unable to retrospectively determine what duration potentially offending medications had been used for.

8. Table 4: Only one patient ceased one drug? No change in drugs? No other drugs that were ceased or changed, e.g., antidepressants, antiepileptic drugs and so on?

Response: Thank you for pointing out the shortcomings of this Table. Diuretics were ceased in 21 patients, where the causative aetiology of hyponatraemia was deemed to be diuretics (+/- other diagnoses) by the treating team. An ACE inhibitor or ARB was ceased in 3 patients. This has been added to the Management section of results. (Page 9, lines 206-209) and Table 4. Unfortunately, cessation of antiepileptics or other medications was not captured during the audit.

9. Table 2: Not sure what the "Not Documented" column stands for. Does it mean that the tests were checked but not documented in the text of the medical files, just in the pathology section?

Response: “Not documented” refers to the patient’s fluid balance not being documented in the chart. The heading in Table 2 and 3 has been altered to better reflect this to “Fluid Status not documented”

10. Was tolvaptan used in any case?

Response: Tolvaptan was not available for use at our institution. This has been added to the management section of results (page 9, lines 218-219)
Response to Reviewer 2: (Rossana Berardi)

Thank you for your comments. Our answers to your points are as follows.

1. Hyponatremia represent the most electrolyte disorder in cancer patients and may be due to the ectopic production of antidiuretic hormone (vasopressin), to extracellular fluid depletion, to renal toxicity caused by chemotherapy or to other underlying conditions. Cancer patients represent a specific subset of hyponatremic patients requiring a specific management; therefore I suggest this concept might be included in the background section among raccomandations[sc] for the treatment of hyponatremia (i.e. Berardi R et al. Hyponatremia in cancer patients: Time for a new approach. Crit Rev Oncol Hematol. 2016 Jun; 102: 15-25. DOI: 10.1016/j.critrevonc.2016.03.010)

Response: Thank you for this suggestion. A paragraph has been added to the Background section regarding the complexity of hyponatraemia in cancer patients. (Page 5, lines 102-105)

2. Data about the age of the patients enrolled in the study are missing, so I suggest to add this data (range and median value) to the text and to insert it in the table 1.

Response: Apologies for this omission. The median age and IQR has been added to the text in the results section (Page 8, line 173). It was not added to Table 1 for formatting reasons, as the data in table 1 are presented as frequencies (N and %).

Response to Reviewer 3: (Christoph D. Schwarz)

Thank you for your careful review. Please find our answers to your questions below:

1. For such a complex disease as hyponatremia the methods of analysis are not explained clearly enough:

As in other studies dealing with hyponatremia it is most difficult to categorize the volume status of the patients. In the method section the authors mentioned that clinical volume status was evaluated. It is necessary to describe the exact criteria used to assess volume status.

Response: Thank you, we agree this is a crucial point. We have clarified how volume status was evaluated by the investigators either by: 1. documentation by the treating team stating the patient was hypo-, eu- or hypervolaemic, or 2. by interpretation of the documented clinical features such
as: vital signs, mucous membranes, skin turgor and presence of oedema. This has been clarified in the Method section (page 7, lines 144-147)

2. Patients were analysed and re-classified..... How were the hyponatremic patients classified by the treating teams? - based on the volume status? or was only the description in the medical records used for classification? It is necessary to describe the terms used i.e. SIADH, hypovolemic hyponatremia,…

Response: The working diagnosis documented by the treating team according to their interpretation of the clinical signs and biochemical investigations was recorded. If no diagnosis was provided then this was recorded as “no diagnosis”. “Hypovolaemic hyponatraemia” was not classified as a diagnosis. This has been expanded in the text. (Page 7, lines 142-149)

3. How was the re-classification done by the study investigators? Were other criteria used to determine eu, hypo and hypervolemia? This is very important for the interpretation of all analysed data.

Response: To reclassify patients into the most likely aetiology of hyponatraemia, documented fluid balance, clinical features and available investigation results were re-analysed by the investigators according to the diagnostic criteria outlined in the European Clinical Practice Guideline of Spasovski et al. (ref 2). (page 7, lines 149-152)

4. A diagnosis of non-renal salt depletion or volume overload was deemed likely if urinary sodium was < 30 mmol/l…..

This is also an inexact definition of two different clinical disorders which have to be separated. It includes i.e. cardiorenal syndromes as well as hypovolemic patients with hyponatremia. It is necessary to make a clear characterisation of all hyponatremic patients based on the available clinical and laboratory data.

Response: Thank you for this suggestion. This has been reworded to more clearly reflect that fluid status as well as urinary sodium values were used to classify patients. (page 7, lines 152-156)

5. Which clinical symptoms were categorized as possible associated with hyponatremia?
Response: Symptoms of hyponatraemia such as headache, nausea and vomiting, confusion, seizures and coma were noted. (Page 7, lines 147-148)

6. How was the duration of hyponatremia estimated as described in table 1?
Response: Duration of hyponatraemia was determined from the serial biochemistry results where available and if available, duration of symptoms from the clinical record. If the duration was unable to determined it was classified as unknown. (Page 7, paragraph 2, line 142-144)

7. Was the hyponatremic episode at admission to hospital or during the hospital stay?
Response: Hyponatraemia identified at any point during an admission was included. (Page 6, line 134-135).