Author's response to reviews

Title: Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis

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Author's response to reviews: see over
Response to reviewers for MS: 1362378621766109 – “Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis”

Bern, September 12th 2012

Dear Dr. D’Souza,

Dear Referees,

We are happy to resubmit our manuscript titled “Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis” to BMC Medicine.

Please find the response to the referees comments below.

We hope that we were able to satisfyingly answer all referees questions.

Sincerely,

Gregor Lindner for the authors
Referee 1

Minor Essential Revisions

1. Abstract, line 4: “…on admission and patient outcome”.
We changed this in the revised manuscript.

Reference 10, Lindner et al Am J Kidney Dis, is correct.

3. Baseline laboratory values other than sodium (100%) and potassium (99%) are reported for only a small percentage of the over 22,000 patients included into the study.
It is certainly true that electrolytes other than sodium and potassium were available for a minority only. However, our analysis focused on sodium and potassium and the information on the other electrolytes were supposed to be supplemental only.

Major Compulsory Revisions

1. Serum creatinine was dosed in 17,813 (80%) out of the over 22,000 patients investigated. As serum creatinine is one of the covariates in multivariate analysis only those patients should be included into the study.
It is true that serum Creatinine was available in 80% of the patients included. However, in the multivariate regression analysis, only patients with a complete data set were included. Since for the pure epidemiology of electrolyte disorders serum Creatinine is not necessary, we would prefer to keep the patients in the analysis.

2. Glomerular filtration rate obtained by the MDRD or the CKD-EPI equation should replace crude serum creatinine in the multivariate analysis.
We calculated the MDRD for all patients. However, since the formula is only validated in patients with renal insufficiency, we decided to use crude serum creatinine.

3. The degree of the electrolytic disturbances should be considered in the data analysis, at least in terms of mild/moderate/severe dysionemia. A linear
A regression model with “quartile” grouping may be used.

As with all electrolytes, the mortality seen in potassium disorders is U-shaped as we do know from other recent studies (e.g. Goyal A et al. JAMA 2012). Thus, we do not believe that this analysis would add further valuable information to our study. However, if wished by the Referee we can perform the analysis and include it in the manuscript.

4. Together with age, gender and GFR, multivariate analysis of outcomes should consider also the main comorbidities requiring specific diuretic therapy, such as hypertension, nephrotic syndrome, liver cirrhosis and cardiac failure.

Unfortunately, we do not have detailed information on patients comorbidities. A case by case review would be necessary for this, which is not feasible due to the large patient number. This limitation is included in the limitations section of the discussion.

Referee 2

Minor comments:

1. Abstract, Background section: Study aims should be given in one clear sentence.

The appropriate changes were made in the revised manuscript.

2. “Thiazides” should be changed to thiazide diuretics.

We changed this in the revised manuscript.

3. I see that it is always a problem in a large study as this, but do the authors have more detailed information on the patients co-morbidities? This information could be of great use.
Unfortunately, we do not have more detailed information on patient comorbidities. A case by case review is not feasible due to the large patient number.

4. **Mean serum potassium was higher in patients under diuretic medication than in those who took no diuretics** (although Hypokalemia was seen more frequently in patients on diuretics, which makes sense). **What is the authors’ explanation for this finding?**

A possible explanation for this finding is that patients taking diuretic medication potentially do so because of renal insufficiency. This hypothesis is supported by the higher mean serum Creatinine in the patients taking diuretics. Our explanation is given in the discussion section of the revised manuscript.

5. **Maybe one or two sentence in the discussion section on the new vasopressin antagonists and their expected impact on electrolyte homeostasis would further improve this section.**

We included a discussion on vasopressin antagonists in the revised manuscript (discussion section).

**Referee 3**

**Major Compulsory Revisions:**

1. **It is not surprising that there is a higher incidence of hyponatremia and hypokalemia in the group that was on diuretics. However, it is very interesting that the incidence of hypernatremia and hyperkalemia was also higher in the diuretic group. In addition, the mean sodium concentration was lower in the diuretic group (138 vs 139). This seems like a very small difference. Taken together, I think these data indicate that the spread of sodium concentrations in**
the diuretic group is much larger than that of the control group. I wonder if this indicates that the control of the serum sodium (i.e. the excretion of free water) is what the problem is. Could this be due to the diuretic itself or possibly due to the underlying disorder.

The spread of serum sodium can be seen by looking at the standard deviation of values (given in the results section - 138±5 vs 139±4 mmol/L). Personally, I do believe that the direct effect by the diuretic agents on renal handling of free water excretion plays a major role, as Referee 3 suggests.

2. The same analysis would apply to the potassium concentrations. The diuretic group had a mean of 4.03 and the control group, 3.93. However, there were more cases of hypo- and hyperkalemia in the diuretic group. Again indicating that the spread (or standard deviation) must be much larger in this group.

Spread of serum potassium was higher in the diuretics group, however, only slightly (4.03±0.63 vs 3.93±0.45 mmol/L). The results are given in the results section.

3. It is not clear in the Kaplan-Meier curve if there is a significant difference.

The difference is significant, which is given in the results section. We included the odds ratios as well as the level of significance in the figure legend of the revised manuscript.

Minor Essential Revisions:

There are a number of references made to reference #1. Since this is a book, it would be helpful for the authors to indicate the chapter or page numbers that are referred to. Otherwise, the reader would need to review the entire text to see the point the authors are making.

In the revised manuscript, we included the reference with chapter name and number.