Author's response to reviews

Title: Change in serum sodium level predicts clinical manifestations of transurethral resection syndrome: a retrospective review

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Author's response to reviews: see over
Responses to Reviewer 1’s comments

Title: Change in serum sodium level predicts clinical manifestations of transurethral resection syndrome

Version: 1
Date: 16 February 2015

Reviewer: Giuseppe Vezzoli

Reviewer's report:
The paper of Ishio et al evaluates serum sodium concentration changes in patients developing transurethral resection syndrome compared with another group of patients who did not develop this syndrome after transurethral prostate resection. The study identifies sodium concentration changes predicting the occurrence of the syndrome.

Major compulsory revisions.
1) The Authors proposed two criteria to define serum sodium changes associated with the transurethral resection syndrome. These criteria do not appear homogeneous to me. The first criterion is a change of 7 mmol/l of the absolute sodium concentration, that is, 5-6% of a sodium concentration between 115-140 mmol/l. The other criterion is a change of 7% of the sodium concentration that is a variation of 8-10 mmol/l of an absolute concentration between 115 and 140 mmol/l.

Response: As the reviewer stated, we investigated three different parameters of serum sodium levels: the minimum sodium level, the change in sodium level, and the percent change in sodium level. We are afraid that we may not have adequately explained what was meant by “change in sodium concentration”. It means the decrease in serum sodium level relative to the minimum sodium level measured preoperatively. The minimum sodium level means the minimum value of serum sodium concentration in each patient in the intra- and post-operative periods. The percent change in sodium level means the percentage of the decrease in sodium divided by the preoperative serum sodium level. We have added a description in the results section to help make this clear. In addition, 7 mmol/l and 7 % change do not relate to sodium concentration between 115 to 140 mmol/l.

We have also added logistic regression analyses for occurrence of symptoms and
showed the results in Table 4. The accuracy for detecting the occurrence of the symptom was similar for absolute change in sodium level and percent change in sodium level.

Minor essential revisions
1) Probably, the Authors have to discuss the different prostate volume and hemoglobin (table 1) in patients developing and not developing symptoms.
Response: We added detail in the results (Page 10, L155-156) and discussion (Page 13 and 14, L225–229) sections about the differences in prostate gland size in Table 1. The value of hemoglobin didn’t show a difference. The difference in hematocrit was not clinically important, so we erased this from our manuscript. The meaning of prostate gland size was vague, so we added detail in the discussion section as follows:

   In the patients’ backgrounds, there was a significant difference between the two groups in preoperatively-estimated prostate gland size. Prostate gland size was preoperatively estimated using ultrasonography, which showed that the patients in the symptomatic group had larger prostates than those in the asymptomatic group: this is in agreement with our previous findings [8].

2) In table 2, it is not clear what “minimum sodium level” is. Probably, it could be better to report the variable as the absolute value.
Response: We added a description of the meaning of “minimum sodium level” and the meaning of “change in sodium level” in the results and discussion sections as follows:

   (Page 10, L159–161) Minimum serum sodium level means the smallest amount of sodium detected in each patient in the intraoperative and postoperative period.
   (Page 10, L168–170) These values were the absolute values in each patient and they were calculated as (preoperative sodium level) – (minimum sodium level). Percent change was calculated as (absolute value) / (preoperative sodium level).

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
Responses to Reviewer 2

Title: Change in serum sodium level predicts clinical manifestations of transurethral resection syndrome

Version: 1
Date: 17 February 2015

Reviewer: Marco Gemma

Reviewer's report:

Dear Authors,

The series at your disposal is very interesting and you address an important issue, namely the serum sodium level associated with TURP syndrome symptoms. Nevertheless the analysis you undertook seems inappropriate. In the “Major Revisions” reported below, I suggest an analysis of your data that could substantially improve your manuscript. Please seek advice of a Statistician, if needed.

Major revisions
1. The Authors aim at studying the predictive value of serum sodium changes on the clinical manifestations of TURP syndrome. In order to accomplish this goal they should build a predictive model that, given the number of possible predictors of TURP, should be multivariate logistic. This is the only way to correctly quantify the relative contribution of natremia to the occurrence of TURP syndrome.

The Authors should precisely describe the possible predictive variables they screen on the univariate variable selection phase. A P<0.25 is the commonly recommended cut-off to maintain variables in the subsequent analysis.

The selected variables should eventually enter a multivariate logistic model, which should be precisely reported, providing single variable Odds Ratios with 95% CI, whole-model P, AUROC, and goodness-of-fit P. In the final model multicollinearity and linearity in the logit of continuous variables should be checked.

A major point is the identification of the dependent variable of such a model. Actually, I think that the “occurrence of any symptom of TURP” is an interesting
dependent variable, but the paper would be much more informative if different predictive models were also provided, one for each TURP symptom.

Among the various examples of this kind of analysis, I suggest one from a completely different setting, namely Agostoni M et al. Adverse events during monitored anesthesia care for GI endoscopy: an 8-year experience. Gastrointest Endosc 2011;74:266-75, in which different logistic regression models are build taking different complications as dependent variables in a retrospective analysis.

Response: We thank the reviewer for this recommendation. We had actually already considered adding the detection of risk factors for symptom occurrence. However, we thought we should have focused on the results of change in serum sodium level, so we eliminated the logistic regression results from our previous manuscript. These have now been added back in to the revised manuscript. Although the reviewer recommended a statistical method with AUROC, we evaluated only using categorical values and have shown the results in Table 4. We made three sets of logistic models. As the reviewer suggested in Major revision #1, we did logistic regression analysis using serum sodium level \( \leq 125 \text{ mmol/l} \), change in sodium level \( \geq 7 \text{ mmol/l} \), and percent change in sodium level \( \geq 7 \% \), respectively. Please see the method section (page 9, L140–147).

2. The Authors consider three potentially predictive variables regarding serum sodium, namely absolute sodium values, absolute sodium changes, and percentage sodium changes. Obviously only one of these variables at a time can enter the same predictive model. A very interesting issue would be which one of these “sodium variables” yields the best predictive model for any given dependent variable.

Following the suggestions in Major Revision #1 reported above, the Authors should provide formal comparison of the AUROC generated by models incorporating different “sodium variables” and addressing the same dependent variable.

Response: As the reviewer suggested, we have tried to show the results of three sets of models. We have added a description in the results and discussion sections as follows:

(Results: Page 11, L176–180) *The logistic regression results are shown in Table 4. We made three sets of models to detect the best predictive variable between absolute sodium level, change in sodium level, and percent change in sodium level. The risk factors for symptoms occurring were sodium level variables, operation time longer than 90 min, and presence of continuous drainage from bladder.*

(Discussion: Page 12, L204–209) *Logistic regression analysis identified the risk factors of symptoms occurring as serum sodium level variables, operation time more than or*
equal 90 min, and presence of continuous drainage from bladder. We evaluated three predictive variables of serum sodium concentration. A sodium level less than or equal to 125 mmol/l was the strictest value, therefore, it was the most reliable parameter. Change in sodium level and percent change in sodium level were similarly reliable parameters.

Minor revisions

1. The Authors use both “TUR” and “TURP” throughout the text. Only one abbreviation should be used and I would suggest “TURP”, which is a standard.

*Response:* We think we have used these abbreviations appropriately, as in our manuscript we have used “TUR” to abbreviate “transurethral resection” and “TURP” to abbreviate “transurethral resection of prostate”. “TURP syndrome” cannot be considered a common word, so we would prefer to keep our present abbreviations, if possible.

2. On P7L107 the concentration of the administered Bupivacaine is missing.

*Response:* We apologize for omitting this information, and have added the percentage of bupivacaine.

3. On P7L110 it is not clear what does “T level” mean. The Authors should provide a precise dermatome level.

*Response:* As the reviewer has suggested, we have added the precise level of thoracic vertebra as “T10 sensory level”. Please see Page 6, L91.

4. 1) The methodology of assessing “cardiovascular and neurological manifestation of TURP” (see P8L122) should be described in details. This is particularly important given the retrospective nature of the study.

*Response:* We agree with the reviewer’s comments that a description of the assessment of these manifestations is very important in this study. We have cited a reference by Hahn et al. in which the researchers used a checklist for cardiovascular and neurological manifestations without seeing serum sodium levels [6]. We have added a new table from this reference. We have changed the manuscript as follows (Page 7, L103–109):

Cardiovascular and neurological manifestations of TUR syndrome were assessed
as described by Hahn et al. [6]. As shown in Table 1, cardiovascular manifestations included chest pain, bradycardia, and hypertension. Neurological manifestations included blurred vision, nausea, vomiting, uneasiness, confusion, tiredness, consciousness, and headache. In the patients of this study, we detected nausea, vomiting, restlessness, confusion, abdominal discomfort, and abdominal pain. As blurred vision, consciousness, and headache were difficult to assess, uneasiness and tiredness were included under the category of restlessness.

4. 2) How were these complications assessed?
The Authors refer to blood pressure “preoperative levels” (P8L124) as a criterion to diagnose hypertension: how and when was it assessed?
Response: “Patients with a > 30 % increase in blood pressure relative to preoperative level” means that the patient showed more than a 30 % increase in blood pressure compared with the preoperative baseline that was measured on the operating bed just before spinal anesthesia was performed. We have added a description as follows to clear this up (Page 7, L110–111):

Patients with a > 30 % increase in blood pressure relative to preoperative levels measured just before local anesthesia was performed in the operating room.

4. 3) How was the differentiation between TURP syndrome and other syndromes (P8L130-1) accomplished?
Response: We have briefly mentioned the differentiation of symptoms between TUR syndrome and other situations on Page 8, L116–118.

5.
The present description of the outcome variable is unclear (P9L147ss): which “neurological score” do the Author refer to? Was it a n/y outcome or an ordinal score? Anyway this item would be corrected if Major Revision 1 was accomplished.
Response: Neurological score was not an established item. We have now defined it to investigate the correlation between serum sodium levels and neurological symptoms. Please see Page 8, L122–124.

6.
It would be interesting to know how many cases exhibited symptoms still having normal serum sodium.
Response: We have added these data as follows (Page 10, L164–166):

In addition, of the 195 patients who maintained a normal sodium level in the intra- and post-operative period, 31 patients showed symptoms. Of the 34 patients with sodium level less than 125 mmol/l, five patients did not show any symptoms.

7.
The manuscript would benefit from good English language revision.

Response: Our manuscript has been edited by a native-English speaker with scientific expertise from an editing company recommended by BMC.

Level of interest: An article of importance in its field

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

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

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