## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Hypotonic and Isotonic intravenous maintenance fluids in hospitalized paediatric patients. A randomized controlled trial |
| **AUTHORS** | Torres, Silvio; Iolster, Thomas; Schnitzler, Eduardo; Siaba Serrate, Alejandro; Sticco, Nicolás; Rocca Rivarola, Manuel |

## VERSION 1 – REVIEW

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| **REVIEWER** | Reviewer name: Michael L. Moritz<br>Institution and Country: UPMC Children's Hospital of Pittsburgh, USA<br>Competing interests: None |
| **REVIEW RETURNED** | 27-Jan-2019 |

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| **GENERAL COMMENTS** | This manuscript compares hypotonic and isotonic maintenance fluids in hospitalized pediatric patients. This topic has been study in numerous other trials, though this study is the first to systematically look at the development of acidosis. It also has one of the largest number of patients < 12 months of age and is the largest done in South America.<br><br>Below are my suggestions for improving the manuscript.<br><br>1. The title should be changed to Hypotonic and Isotonic intravenous maintenance fluids in hospitalized paediatric patients: A randomized controlled trial.<br>2. In the abstract the objective should state compare the changes in serum sodium and acid/base status in patients receiving hypotonic and isotonic solutions.<br>3. The study should actually look at the changes in serum sodium, the incidence of mild hyponatremia < 135 and moderate hyponatremia < 130, the incidence of hypernatremia > 150 and acidosis pH < 7.3.<br>4. Hour 1 and 2, should be changed to T12h and T24h as this is more clear for the reader.<br>5. The results section has the incidence of hyponatremia backwards. It should be 18.8% and 8.3%, not the other way around. Also the authors need to be consistent throughout the paper presenting data on hyponatremia first and isotonic fluids second.<br>6. RR should be 3.717 and not 3,717.<br>7. The predictive model of hyponatremia does not seem to be helpful to the reader. It may be better to just state identified risk factors associated with hyponatremia.<br>8. In the conclusion of the discussion, the mention of clinical correlate should be removed as it is not clear what this means. They probably mean to say that neurologic complications did not develop.<br>9. In the introduction it should read chloride and not chlorine.<br>10. While not available at the time that this manuscript was submitted, the American Academy of Pediatric Clinical Practice Guideline on Intravenous Fluid Therapy now needs to be referenced ad acknowledged. |

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| | The CPC states that future studies are needed to assess the development of acidosis and this study nicely addresses that.<br>11. In the methods section it is not clear what lab studies were collected at T0, T12 and T24. Did all patients have a blood gas at these three time periods? If so this is very important data that needs to be displayed and discussed prominently as I am not aware of any studies there true acid base status by VBG was systematically evaluated.<br>12. It says than urine osm >100 and weight change of >2% was an exclusion criteria. It is not clear why those would be exclusion criteria. I also does not state that urine osmolality or weights were monitored. If fluid overload was detected then that should be reported as and adverse event. There should be section about adverse events in the study.<br>13. In table 1 sodium values are reported and median and range, but in table 2 it is reported and mean and SD. Median and range is the preferred way of reported data that is not normally distributed and table 2 should be changed.<br>14. Table 2 should also have patient with moderate hyponatremia < 130 and hypernatremia > 150.<br>15. Table 2 should have pH values reported at T12 and T24 and there should be statistical analysis if there was an increase in acidosis at T12 and T24 compared to baseline. It could be that acidosis does develop in both fluids as they are both acidogenic.<br>16. There are variety of meta-analysis that have been reported assessing the incidence of hyponatremia and the RR of this study should be compared to those studies. |

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| **REVIEWER** | Reviewer name: Eirini Koutoumanou<br>Institution and Country: UCL, UK<br>Competing interests: None |
| **REVIEW RETURNED** | 06-Feb-2019 |

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| **GENERAL COMMENTS** | This is a well written report with a clear question and a clear description of the methods used to answer this question.<br><br>Firstly, the main thing that left me wondering after reading this report, was why the authors oversampled so much over the minimum size indicated by the power calculation? Instead of 50 in each group they sampled over 140 in each. Also, apart from the info presented in the text regarding the power calculation, the minimum expected % for one of the groups is required – what was the value used for this?<br><br>Secondly, I would recommend that the authors perform sensitivity analysis regarding the fitted regression model where some of the univariately non-significant terms are also added on the multivariable model. Regression models have the ability to identify relationships that are only visible when several related explanatory variables are considered at the same time, even if they are univariately not significant. Similarly, the LOS differences could be further explored/adjusted via a regression model even though they came out no significantly different univariately.<br><br>Finally, did the authors consider analysing the 12h and 24h serial measurements via repeated measures analysis? This could form again part of sensitivity analysis section to ensure no differences have been missed. |

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| | Minor:<br>- I would recommend moving Table 1 at the results section.<br>- The value of the RR before Table 3 should be corrected to 3.77 instead of 3,77.<br>- Please replace the term multivariate with multivariable, as per the references below<br>- A couple of syntax corrections are required in the 3rd paragraph of the introductory section. Also replace march by March.<br>- The 4-fold increase in the risk cited at the beginning of the Discussion section should be referred to as unadjusted as this number changed quite a lot after the logistic regression adjustment.<br><br>References:<br><br>Peters, T. J. (2008), Multifarious terminology: multivariable or multivariate? univariable or univariate?. Paediatric and Perinatal Epidemiology, 22: 506.<br>doi: 10.1111/j.1365-3016.2008.00966.x<br><br>B Hidalgo and M Goodman (2013), Multivariate or Multivariable Regression? American Journal of Public Health, Vol. 103, No. 1, pp. 39-40.<br>doi: 10.2105/AJPH.2012.300897 |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1:

1- We have changed the tittle as suggested to make it more clear and significant.

2- We have added changes in the abstract regarding analysis of the acid/base status.

3- We have differentiated mild Hyponatremia from moderate hyponatremia in the analysis

4- We have changed T1 and T2 for 12 hrs. and 24 hrs. as suggested

5- We have changed the way data is presented as suggested by reviewer

6- We have changed 3,71 for 3.71.

7- We improved the way the risk factors of hyponatremia are presented

8- We removed the term ”clinical correlate” from the discussion/ conclusion.

9- We have changed for chloride.

10- We added a paragraph about the new pediatric maintenance intravenous fluids guideline in the discussion regarding the incidence of acidosis with isotonic fluids.

11- The periods for the lab studies are defined as 0, 12 and 24 hrs in the methods section.

12- This point is a weakness of the study, we did not collect clinical data of fluid overload. We agree that it would have added useful information.

13- We agree with the reviewer and changed for median and range in all the tables.

14- We added patients with moderate and mild hyponatremia. We don't have patients with hypernatremia.

15- We added the PH values in table 2 at 12 and 24 hrs.

16- We compare our RR value with an important meta-analysis in the discussion section

Reviewer 2:

1- We thought that the oversample would help to obtain more accurate information.

2- We carried out a Hosmer –Lemeshow Test and ROC curve to test sensitivity and specificity of the model and its capacity of calibration and discrimination. For the multivariable regression, we included significant and non-significant variables. Finally in the predictive model we mention the significative variables.

3- We analyze the global 12 and 24 hrs. in the multivariable analysis, but not individualy. That is a weakness of our study, we agree that it could form part of a sensitivity analysis.

4- We have moved Table 1 to the results section

5- We corrected the RR value to 3.77.

6- We replaced the term multivariate for multivariable.

7- We replaced by March.

8- The risk changed after the multivariable analysis. We modified this number in the discussion section.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Reviewer name: Michael Moritz<br>Institution and Country: University of Pittsburgh School of Medicine. UPMC Children's Hospital of Pittsburgh<br>Competing interests: None |
| **REVIEW RETURNED** | 19-Mar-2019 |

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| **GENERAL COMMENTS** | The revisions have made the manuscript much better and more clear. The manuscript does need to be edited by an English speaker though. Below are some edits that need to be made.<br>When the term natremia is used the proper term should be sodium<br>When glicemia is used the proper term is glucose<br>In table 1 post-transplant of bone marrow should be post bone marrow transplant<br>For the three surgical groups of patients it should say Post-surgical with subheading of neurosurgical, thoracic, abdominal.<br>Convulsive syndrome should be seizure disorder<br>In Table 2 for mild hyponatremia add (Na < 135) and for moderate hyponatremia add (Na M 130) for metabolic acidosis add (pH <7.3)<br>Later in the manuscript change thorax to thoracic<br>In the acknowledgement change confection to conception |

## VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

- We replace the terms as the reviewer suggested: sodium, glucose, post bone marrow transplant, post-surgical (Table 1), seizure disorder (Table 1), mild and moderate hyponatremia (Table2), metabolic acidosis (Table2). We also changed for the terms thoracic and conception.