Reviewer's report

**Title:** Comparison of Clinical and Biochemical Markers of Dehydration in Children: A Prospective Double-cohort Trial

**Version:** 1  **Date:** 28 February 2014

**Reviewer:** Amanda B Hassinger

**Reviewer's report:**

Major Compulsory Revisions:

1. **Title:**
   a. Please amend to include the CDS as it seems to be the study's primary focus.

2. **Abstract:**
   a. The methods section does not define what is meant by “dehydration.” This is an important clinical term to this study as it is used for both the inclusion criteria and the outcome measure.
   b. The conclusion is too much of a jump. Bicarbonate is not the gold standard for dehydration even though this study found the highest correlation with dehydration. The conclusion also should not present new data not included in the results.

3. **Background:**
   a. Please provide more information about the three prospective studies which have validated the CDS including number of patients, age groups, year of publication, etc. This is essential to proving the need for this current study.
   b. What is meant by “reliable” control group? This should be expounded upon as it provides the central argument for the importance of this study.
   c. The primary study hypothesis does not clearly state why there was a control group. It is unclear why a control group without dehydration was used if the study is primarily designed to investigate the hypothesis “that the CDS would correlate with standard biochemical markers for dehydration.”
   i. It is implied the control group is being used to validate the biomarkers and then the biomarkers are being used to validate the CDS. Is this the study's design?

4. **Materials and Methods:**
   a. The choice of cases and controls needs more explanation:
      i. The choice of a trauma “control” group could affect a few of the dehydration markers being studied, specifically the heart rate and some urinary markers especially if the patient had any unidentified renal or head trauma which could impair sodium handling, acid base balance, cause tubular damage or lessen GFR. Were there any additional exclusion or inclusion criteria for the controls?
      ii. Cases were identified as those who were found to have a gastroenteritis and
“dehydration.” Dehydration has to be more clearly defined. How exactly was this determined by the screening research nurse?

1. Was there validation of the screening nurse’s determination that the cases were indeed dehydrated? What criteria did she use? This is essential to ensure there was no case misclassification.

b. Need to discuss why inter and intra-observer error was not assessed in the CDS scoring in a study about a subjective rating scale.

c. Please outline all biomarkers used as surrogate markers of dehydration with references supporting their use as “established biochemical surrogate markers of dehydration.”

d. When performing ROC analysis, one should be specific about the binary outcome of interest. I assume the outcome being tested is the presence of absence of dehydration per initial screening but this should be explicitly stated.

e. Please specify if you performed spearman or Pearson correlation analyses.

5. Results:

a. Please be clearer about what the ROC analysis was testing predictability for. It is standard to also include the 95% CI and the p-value for every ROC curve. If you are comparing the groups, then this analysis is complicated by the fact that there was not a difference in percent dehydration between those with dehydration and your controls.

b. Why was no correlation analysis performed on the CDS and percent dehydration, which is what the scale was designed to predict?

c. Please comment on the urine-production status of the patient with HUS as some readers may assume that patients needing dialysis may be oliguric or anuric and, therefore, not clinically dehydrated at all, but more fluid overloaded.

6. Discussion:

a. There was no statistical difference between percent dehydration in the dehydrated patients when compared to controls. This raises significant questions as to the validity of this study, i.e. were the cases and controls truly different enough to validate a scale of dehydration?

b. The difference in blood urea which is statistically significant is not clinically significant and should not warrant much comment.

c. If the author’s statement that the CDS was validated against serum bicarbonate in its inception, then the authors cannot use serum bicarbonate to indirectly validate the CDS as seen in the second paragraph on page 12.

d. The paragraph discussing the potential for selection bias is important but muddled. In this manuscript, there is insufficient support for the statement: “First, our selection criteria biased our dehydration group to children with more severe disease.” This is also contradicted by the authors’ later comments that parental hydration is started more often than oral despite oral hydration’s superiority. Please clarify if the authors argue that patients with dehydration who receive intravenous fluids are more severely ill or not.
e. If the CDS is not validated for children over 5 years of age as outlined in the top paragraph on page 13, why were older children included? The control group’s median age was 8 years old. The dehydrated patients were within the appropriate age group. If CDS was used to prove the controls were not dehydrated; however, the scale was not intended for children over 5, how can the authors reliably ensure the controls were indeed hydrated?

f. Please comment on the age difference as a potential confounder for the difference in blood urea and serum creatinine concentrations seen between the cases and controls. Heart rate could also be influenced by other factors in younger rather than older children who are more anxious in a health care setting.

g. The use of percent dehydration in this study meets many challenges:
   i. The authors have to address the fact that post-hydration weights were only available on 60% of the dehydrated group and this weight was needed to calculate the true percent dehydration which would be the only non-subjective outcome for hydration used in this study.
   ii. Why didn’t the pre and post-hydration weights change in the patients with dehydration if the HR, systolic and diastolic z-scores declined? In fact, weight z-scores declined in both groups implying patients lost weight, as commented on in the discussion. These things are incongruous with physiology: why would the systolic blood pressure and weight go down after hydration? One plausible reason may be that the patients did not have intravascular dehydration upon presentation.
   1. Why would trauma patients lose weight after treatment? This calls into question the validity of any of the weights done in this study.
   iii. The discussion on page 13 which concludes that percent dehydration is a “subjective parameter” is incorrect. The parameter is objective as it relies only on actual measured data. It may not reflect hydration status as the rest of the paragraph describes, but the parameter itself not subjective. The other variables used in this study such as the CDS score and MRPs assessment of hydration are subjective and therefore need validation with inter-rater reliability testing.
   iv. This discussion has to include the possibility that the dehydrated patients were not all truly dehydrated as no gold standard was used to classify the cases and the controls. Or that the controls were not all hydrated. The urinary osmolality of the controls speaks against being well hydrated.

Not included in the Discussion but needs to be:

h. Please explain the incongruity inherent in the concept that a CDS score of 0-2 was considered “mild” dehydration for the cases however the argument was made that a CDS of 0 for the controls proves they were not dehydrated. Even if every patient in the control group scored a 0 on the CDS, there were patients in the dehydration group whom also scored a 0 and were considered “mildly” dehydrated.

Minor Essential Revisions:

1. Abstract:
a. The background implies that the CDS is a well-known tool. Needs more explanation to those who are not familiar with it.
b. The statistics are incorrectly described and presented in the methods and results sections:
   i. Is that the median with the total range or interquartile 1-3 range?
   ii. P-values are necessary to describe differences between the groups in terms of age and CDS.
   iii. The sentence starting with “Difference in heart rate” needs to be more specific about what you are comparing. It is assumed that it’s the control and the dehydrated groups, but it has to be expressed. This sentence is also grammatically incorrect (Difference… were).
   iv. When presenting a correlation, the correlation coefficient not just the p value should be shown.
2. Background:
   a. The sentence starting with “It is also the most common cause” needs to state in which population this is true.
   b. Need a reference for the second half of the sentence starting with “Although previous studies…”
3. Materials and Methods:
   a. Technically this is a case control study since patients were chosen based on their disease status.
   b. Please specify what ages were included.
   c. Why did you not exclude patients with a sodium derangement?
   d. Please specify when the attending physician conducted the CDS scoring, was it always before any fluid was administered?
4. Results:
   a. Please remove “experimental” from the sentence starting with “seventy-three” as this implies an intervention was performed.
   b. Please insert p-values after each comparison offered in the text.
   c. Would comment on the lack of a gold standard for dehydration.
   d. The Material and Methods section reports that a correlation coefficient of >0.8 would be considered significant however the results conclude the coefficient of -0.355 was significant for the association between serum bicarbonate and CDS. Please discuss this discrepancy either in the results or discussion.
5. Discussion:
   a. Cannot conclude “Friedman’s CDS scoring system is a useful clinical tool.” This is anecdotal and was the entire point of the study. Would remove this sentence or rephrase.
   b. Please remove “anecdotal” from the 4th sentence of the second paragraph on page 12. It is more appropriate to simply state if an association existed or not.
c. Also, the authors should discuss what is the clinical utility of a tool to determine dehydration if it does not lead to important morbid outcomes like LOS, admission, etc.

d. What is meant by “the likelihood of complications” as there is neither intervention from the study nor any specific therapy which would cause complications which would impact results?

e. Please explain what the clinical significance is of the urinary micro-albumin/creatinine ratio and the urinary a1-microglobulin/creatinine ratio.

6. Tables/Figures:

a. Figure 1: Initial number in the top box, 29, must be a typo. The text lists that as “229” patients.

b. Table 1:
   i. Please include the n for each group in the header.
   ii. Are you presenting the total range or interquartile ranges with the median values?
   iii. Statistical analysis of the weight, systolic, diastolic and HR changes pre and post-treatment inside of the groups is important as well to prove that the dehydrated patients were adequately hydrated and the control patients were not dehydrated. The results presented in the text should be somehow included on this table.

c. Table 2:
   i. Please include the normal values for these markers, the control group cannot be assumed to be “normal.”
   ii. The sentence starting with “Data from the control group” is not essential to that table nor is it phrased in a way that implies understanding of ROC curves and should be removed.

Discretionary Revisions:

1. Abstract:
   a. Would mention which direction the differences are in heart rate, diastolic BP, etc. between groups.

2. Background:
   a. The sentence beginning with “When assessing a patient” is too wordy and awkward. It should be reworded.
   b. Table to illustrate how to calculate the CDS would be extremely helpful for others to use this tool if they are convinced by this article.

3. Materials and Methods:
   a. The sentence starting with “Results in this current article” is worded poorly and should be rewritten for clarity.
   b. Would include how many MRPs were included in the study to give the readers a sense of how many different opinions would be forming the subjective
hydration status and be performing the CDS.

4. Results:
   a. Presenting the height data does not add anything to the results.
   b. Giving actual heart rates and blood pressure values would be helpful for clinical utility and translation to physician readers. The Z-score is excellent but not as helpful to the reader immediately.
   c. Remove “Apart from comparing cohorts” from the first sentence of the second paragraph on page 10. Too anecdotal.
   d. Performing the ROC curve analysis to determine the predictability of serum bicarbonate and CDS for each strata of dehydration would strengthen the study’s findings.
   e. The amount of fluid resuscitation provided to the cases and controls would be helpful information. In fact, looking at the IVF boluses given to each strata of dehydration would strengthen the argument that these patients were indeed more dehydrated.
   f. It could also potentially strengthen the results to re-analyze the data excluding any patients who are missing important data as mentioned at the bottom of page 8.

5. Discussion:
   a. The last few sentences in the final paragraph of the discussion feel “tacked on” and do not add to the strength of the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.