Author's response to reviews

Title: Use of a blood gas analyzer and a laboratory autoanalyzer in routine practice to measure electrolytes in intensive care unit patients

Authors:

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Author's response to reviews: see over
Dear editor;

We tried to make the corrections asked by the reviewers. We highlighted the changes in manuscript.

Sincerely.

Yasemin Budak

Reviewer: volkher scharnhorst

1- Cl- is not mentioned in the manuscript but should preferentially be included as it is important for assessment of electrolyte and acid-base status of patients.

We couldn't add.

2. The ABG measures—on average—5 mmol/L lower Na than the AA. No explanation for that observation is suggested. The AA is traceable to flame photometry. Nothing is stated about calibration of ABG. It's probably calibrated with a NIST standard which leads to lower results. Furthermore, different types of heparin in blood gas syringes may introduce different negative biases in the measurement of positively charged ions. What is known about the syringe used here?

The authors need to elaborate on both points.

We add.

The observed differences between electrolyte levels measured using an ABG and an AA may be explained by a combination of factors, including sample transport, dilution of serum samples prior to testing (thus, the use of indirect vs. direct electrodes), and variations in instrument calibration [16, 17]. It is known that ISE-based instruments from different manufacturers yield Na⁺/K⁺ values that differ by 2–5%; calibration of an AA using a NIST standard lowers the figures [18]. Also, it has recently been reported that the use of different types of heparin in blood gas syringes can introduce a pre-analytical bias in electrolyte
concentrations. Such syringes can introduce different negative biases when the levels of positively charged ions are measured. The extent of bias differs among syringe types [19, 20]. Our patients were all critically ill in the intensive care unit (ICU). Chow et al. [14] reported that direct ISE sodium and potassium figures were lower than those obtained using indirect ISE. This is associated with the low blood protein levels characteristic of critically ill patients.

4. The imprecision and accuracy data in the manuscript do not serve their purpose well. Your key point is (lack of) agreement between two methods. Imprecision and accuracy are only relevant in whether they explain the differences observed between the methods (they don't). Furthermore you do not present external accuracy data for the ABG. Therefore, for accuracy I suggest you state in the discussion section that the AA performs well in external QC schemes (and that you do not have that data on the ABG). Thereby the focus is more on agreement rather than on accuracy (which you didn't investigate).

We add the following section and also tried to focus on agreement.

To ensure the accuracy of test results, our central laboratory (employing an AA) participates in an external quality assessment (EQA) program; both electrolytes were assayed with reasonable accuracy during the study period. However, the accuracy of ABG data was not evaluated via any EQA program; this is an important limitation of the present study.

5. Section 'study population': the authors mention 1,105 tests. What is meant by tests? Both electrolytes together, number of blood gas samples analyzed? Sum of all tests in all samples included. Please clarify.

We tried to correct.

We studied patients who had been hospitalized in the ICU for some time in the interval between July and August 2011. We identified 84 instances, of 1,105 patient blood gas samples analyzed, in which arterial and venous samples were collected simultaneously and Na$^+$ and K$^+$ were measured using two methods.
6. The part ‘Analytical imprecision of Na and K determinations’ of the manuscript also deals with the accuracy of the lab analyzers. That should be reflected in the title of that part. I suggest that the part dealing with the accuracy of the lab analyzer in the external quality control scheme should be presented in a more compact way.

We tried

**Analytical precision of Na\(^+\) and K\(^+\) determinations**

Before data analysis, we ran a two-level quality-control (QC) test using materials supplied by the manufacturers of both devices (Stat Profile pHox Plus Control 1, 2; Lots 011004 and 011005, and PreciControl ClinChem Multi 1; Lots 158565 and 158577). The reproducibility of results obtained throughout the study was evaluated via analysis of duplicate QC samples on each of 20 days (between-day differences were calculated) (Table 1). For quality assurance purposes, our laboratory participates in the Riqas external quality assessment scheme; Cycle 8 (Samples 7-8) ran during the study interval. The mean comparative K\(^+\) level was 4.19 mmol/l whereas our figure was 4.20 mmol/l; the mean K\(^+\) level was 6.04 mmol/l whereas our figure was 6.35 mmol/l; the mean Na\(^+\) level was 143.71 mmol/l whereas our figure was 144.0 mmol/l; and the mean comparative Na\(^+\) level was 157.18 mmol/l whereas our figure was 155.0 mmol/l.

7. Paragraph ‘statistical method’: It is of no practical consequence here, but taking a p value <0.001 as statistically significant is very strict.

Because it doesn’t effect the results, We changed it to p<0.05.

p<0.05 was considered statistically significant.

8. Did you assess whether Na and K values are normally distributed; if not median values and percentiles should be used instead of mean and SD.

We assessed before, but we added the sentence.

Data were tested for normality using the Kolmogorov-Smirnov test.
9. Is a difference of 0.2 mmol/L clinically relevant when relevance is based on intra-individual variation? Please state that in the manuscript.

The mean between-assay difference in K⁺ levels was 0.25 mmol/L. Although the mean difference between the results of the two K⁺ assays was within the range given by the US CLIA 1988 guidelines [10], a difference of 0.25 mmol/l is clinically relevant when intra-individual variation is considered. When it is recalled that the intra-individual biological variation in K⁺ level has been reported to be 4.8% [15], the bias between both methods did not exceed the acceptable level of inaccuracy [15]. It is important to emphasize that the cited criteria are very strict; the acceptable inaccuracy in terms of potassium measurement is only 1.8% [15].

10. ‘reliability’ should be replaced by accuracy.

We did.

11. You should add a section stating that in every institution agreement between central and POC analyzers should be assessed before installation of POCs instrument and clinically relevant differences may not exist.

Ideally, before installation of an ABG, it would be useful to carefully evaluate the clinical significance of any difference between data yielded by central laboratory devices and POCT instruments. Such an evaluation should be conducted prior to ABG installation; this was unfortunately not the case in our hospital. Individual laboratories should utilize external NICS Standard SRM 956 to verify calibrations conducted by manufacturers and to ensure that the results afforded by direct and indirect ISEs [18] do not differ to a clinically relevant extent.

12. Table 1:

Why do you state between-run and not-overall CV? It is the last CV that determines whether imprecision may explain the differences between AA and ABG.

Because the study was a retrospective data analysis we didnt have the within-run and overall CV fort hat study period.
Why do you state the target (I guess derived from the package insert)? The table presents data on imprecision?

We omitted the target values which we got from the package insert.

The reproducibility of results obtained throughout the study was evaluated via analysis of duplicate QC samples on each of 20 days (between-day differences were calculated) (Table 1).

The %CV of AA and ABG are equal on all controls? I guess that is an error?!

We corrected, yes it was a copy paste error.

13. Figures

Figure 1. Data are presented with mmol intervals, why is that?

I made it by the programme Analyse-it, and I think this is ok.

Figure 2 and 4. Identity lines (y=x) should be added so the reader can easily see whether the regression lines lie above or below the identity lines.

I couldnt do it my analyze-it version

Reviewer: Paul D'Orazio

1. The authors conclude that values obtained using blood gas analyzers are not completely reliable in terms of clinical decision making (4th paragraph of Discussion) and central laboratory results should be used, in preference to POCT data, when critical management of therapeutic decisions must be made (final paragraph of Discussion). These conclusions are in disagreement with previously published reports (references 4 and 14) which conclude that direct ISE results reflect electrolyte activity more accurately than indirect ISE because direct ISE are not sensitive to changes in plasma water content due to high or low protein concentration, etc. Data in reference
14 show reported direct ISE data for sodium and potassium to be lower than indirect ISE, in agreement with the authors' data, related to low protein concentrations as might be found in critically ill patients. The authors should explain why their conclusions are in disagreement with earlier publications.

We changed the 4th paragraph.

Our data are in line with those of previous studies [11-14] showing that Na$^+$ values obtained using two different types of measurement differ significantly, and to an extent that may affect therapeutic choice. Our patients were all critically ill in the intensive care unit (ICU). Chow et al. [14] reported that direct ISE sodium and potassium figures were lower than those obtained using indirect ISE. This is associated with the low blood protein levels characteristic of critically ill patients.

We changed the final paragraph.

In conclusion, Na$^+$ and K$^+$ test results obtained using an ABG and an AA differ and the data thus cannot be used interchangeably in clinical practice. Physicians need to be aware of between-assay differences to avoid potential misdiagnosis and initiation of unnecessary treatment or investigation.

2. The authors should include data for protein concentration, if available, for their study population to attempt to explain differences in the sodium and potassium data between the two methods.

Because these are retrospective data we couldn't find protein data for most of the patients at the exact same time their Na and K were recorded.

3. The authors need to support their conclusion of better accuracy for the indirect ISE device with some reasoning. Is it because Na$^+$ and K$^+$ reference intervals at their institution are based on this type of device, or other rationale?
We changed discussion section and the last paragraph and focused on the lack of agreement between the methods instead accuracy of one of them, because you are right we donot have enough data to rationale.

Minor Essential Revisions

1. Statement of approval of the study by ethics committee should be move from its present location in the text to the section titled “Study population”.
   
   We did.

2. Reference 16 is a repeat of reference 3 and could be omitted.
   
   We did

3. The title of Table 1 should be changed to include the fact that the measurements shown are for quality control materials.
   
   We did.

4. The word "linear" is misspelled throughout the manuscript.
   
   We did.

Discretionary Revisions

The authors state at the end of the Discussion section that it is not possible to establish whether the central laboratory or ABG values were closer to the true values for either analyte. Standard Reference Material (SRM 956), based on human serum and with Na+ and K+ values assigned by the definitive method, is available from the US National Institute for Standards and Technology (NIST) for this purpose. The authors may consider using this material to test accuracy of their methods.

We added:

Ideally, before installation of an ABG, it would be useful to carefully evaluate the clinical significance of any difference between data yielded by central laboratory devices and POCT instruments. Such an evaluation should be conducted prior to ABG installation; this was unfortunately not the case in our hospital. Individual laboratories should utilize external NICS
Standard SRM 956 to verify calibrations conducted by manufacturers and to ensure that the results afforded by direct and indirect ISEs [18] do not differ to a clinically relevant extent.