Bias in the Determination of Dialysate Sodium Concentration Set According to Conductivity Relative to Indirect Ion-Selective Measurement Techniques

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Dialysate sodium is traditionally set at a constant in the range of 136 to 140 mmol/l, with the intention of providing isonatric dialysis.1 Increasing dialysate sodium can potentially decrease intradialytic hypotension and symptoms such as cramps but may also result in transfer of sodium to the patient with consequent increased thirst, higher intradialytic weight gain, hypertension, and volume overload.2–5 Lowering dialysate sodium may lead to reduced thirst, lower interdialytic weight gain, and lower systolic blood pressure with subsequent beneficial effects on left ventricular morphology,5 but at the same time may make intradialytic fluid removal more challenging. An individualized dialysate sodium prescription, set to achieve a zero sodium gradient between dialysate and serum, has been reported to decrease thirst, interdialytic weight gain, and predialysis blood pressure.2,5,6 Paradoxically, for clinical outcomes, observational data from Dialysis Outcomes and Practice Patterns Study (DOPPS) suggest lower mortality with higher dialysate sodium.1 Nevertheless, altering the sodium concentration in the dialysate is used as a strategy for volume and blood pressure management,3 and a large cluster randomized trial is ongoing to provide better evidence in this area.7,8 These modulations of dialysate sodium are made by adjusting dialysate conductivity, as sodium is the primary driver of conductivity. Approximately 1-Ms/cm change in conductivity corresponds to approximately 10 mEq/l of sodium.4–5,7 Dialysis machines alter dialysate conductivity primarily by volumetric measures (i.e., they modulate the dilution of acid concentrate to achieve a particular dialysate conductivity).

There are some reports that the actual measured dialysate sodium concentration may vary from the ordered dialysate sodium concentration.5 This may have implications for clinical care as well as for the planning and interpretation of clinical studies assessing the impact of dialysate sodium adjustments. We designed this quality assurance study to measure the bias between machine-reported conductivity and dialysate sodium measured using a standard indirect ion-selective (ISE) technique and to determine the factors associated with the bias, if present.

RESULTS

Data are presented from 196 measurements taken from 50 simulated dialysis sessions in which dialysate sodium was measured using the plasma mode and 35 measurements taken from 7 simulated dialysis sessions in which dialysate sodium was measured using the urine mode.

Overall, when analyzed using the plasma mode, the measured sodium was significantly higher than the set dialysate sodium (i.e., set according to conductivity), with an average difference of 6 mmol/l (± 1.6 mmol/l, 95% confidence interval [CI], 5.9–6.3).

The difference between set and measured sodium was consistently higher across all subgroups (Table 1). Within subgroups, there was no difference between 135 and 140, either as set dialysate sodium or at different time points during dialysis. However, the difference was greater with 2K bath (as compared to 3K bath), with central dialysate (compared to jug), and between different dialysis machine models.
The difference was smallest with the Fresenius 4008 (5.1 ± 1.9 mmol/l) than the Gambro Artis (6.0 ± 1.4 mmol/l) or the Belco Formula (7.0 ± 1.0 mmol/l).

When analyzed using the urine mode, the difference between the measured sodium and set dialysate sodium was significantly lower than with the plasma mode (average difference 1.5 mmol/l (± 2.9 mmol/l, 95% CI, 0.6–2.9). It remained statistically higher than the set dialysate sodium (i.e., set according to conductivity). The difference between set and measured sodium was not significantly different across the subgroups (Table 1).

**Table 1. Prescribed (set) versus measured dialysate sodium**

|        | n   | Set sodium | Measured sodium | Difference | P valuea | P valueb |
|--------|-----|------------|-----------------|------------|----------|----------|
| Plasma mode |     |            |                 |            |          |          |
| Overall | 196 | 136.5 ± 2.3 (136.2–136.9) | 142.6 ± 2.7 (142.2–142.9) | 6.0 ± 1.6 (5.9–6.3) | <0.001   |          |
| No bath |     |            |                 |            |          |          |
| 135    | 136 | 135        | 141.1 ± 1.2 (140.9–141.3) | 6.1 ± 1.2 (5.9–6.3) | <0.001   |          |
| 140    | 60  | 140        | 145.9 ± 2.2 (145.3–146.4) | 5.9 ± 2.2 (5.3–6.4) | <0.001   |          |
| K bath |     |            |                 |            |          |          |
| 2K     | 117 | 136.8 ± 2.4 (136.3–137.2) | 143.0 ± 2.7 (142.6–143.5) | 6.3 ± 1.8 (6.0–6.6) | <0.001   |          |
| 3K     | 79  | 136.2 ± 2.2 (135.7–136.7) | 141.8 ± 2.6 (141.3–142.4) | 5.6 ± 1.0 (5.4–5.9) | <0.001   |          |
| Dialysate |     |            |                 |            |          |          |
| Central | 40  | 137.5 ± 2.5 (137.6–137.8) | 144.3 ± 2.6 (143.5–145.2) | 6.8 ± 1.0 (6.5–7.1) | <0.001   |          |
| Jug    | 156 | 136.3 ± 2.2 (135.9–136.6) | 142.1 ± 2.5 (141.7–142.5) | 5.8 ± 1.6 (5.6–6.1) | <0.001   |          |
| Model  |     |            |                 |            |          |          |
| Fresenius | 40  | 135.5 ± 1.5 (135.0–136.0) | 140.6 ± 1.0 (140.3–141.0) | 5.1 ± 1.9 (4.5–5.7) | <0.001   |          |
| Gambro  | 116 | 137.4 ± 2.5 (137.0–137.9) | 143.4 ± 3.1 (142.9–144.0) | 6.0 ± 1.4 (5.8–6.3) | <0.001   |          |
| Belico  | 40  | 135        | 142.0 ± 1.0 (141.7–142.3) | 7.0 ± 1.0 (6.7–7.3) | <0.001   |          |
| Time, h |     |            |                 |            |          |          |
| 0      | 49  | 136.5 ± 2.3 (135.9–137.2) | 142.6 ± 2.9 (141.8–143.4) | 6.1 ± 1.6 (5.6–6.5) | <0.001   |          |
| 1      | 49  | 136.5 ± 2.3 (135.9–137.2) | 142.3 ± 2.7 (141.6–143.1) | 5.8 ± 1.7 (5.3–6.3) | <0.001   |          |
| 2      | 50  | 136.8 ± 2.4 (135.9–137.3) | 142.5 ± 2.5 (141.9–143.3) | 5.9 ± 1.6 (5.5–6.4) | <0.001   |          |
| 4      | 48  | 136.4 ± 2.3 (135.8–137.1) | 142.8 ± 2.7 (142.0–143.5) | 6.3 ± 1.4 (5.9–6.7) | <0.001   |          |
| Urine mode |     |            |                 |            |          |          |
| Overall | 35  | 138.6 ± 2.3 (137.8–139.4) | 137.0 ± 3.5 (135.8–138.2) | 1.5 ± 2.9 (0.6–2.4) | 0.001   |          |
| No bath |     |            |                 |            |          |          |
| 135    | 10  | 135        | 133.3 ± 3.1 (131.1–135.5) | 1.7 ± 3.1 (0.5–3.9) | 0.11    |          |
| 140    | 25  | 140        | 138.5 ± 2.4 (137.5–139.5) | 1.5 ± 2.4 (0.5–2.5) | 0.006   |          |
| K bath |     |            |                 |            |          |          |
| 2K     | 10  | 140        | 139.6 ± 2.1 (138.1–141.1) | 0.4 ± 2.1 (1.1–1.9) | 0.55    |          |
| 3K     | 25  | 138.0 ± 2.5 (137.0–139.0) | 136.0 ± 3.5 (134.6–137.4) | 2.0 ± 0.5 (0.9–3.1) | 0.001   |          |
| Model  |     |            |                 |            |          |          |
| Fresenius | 15  | 140        | 137.3 ± 2.2 (136.1–138.5) | 2.7 ± 2.2 (1.5–3.9) | <0.001   |          |
| Gambro  | 5   | 135        | 134.4 ± 0.5 (133.7–135.1) | 0.5 ± 0.2 (0.1–1.3) | 0.07    |          |
| Belico  | 15  | 138.3 ± 2.4 (137.0–139.7) | 137.7 ± 4.7 (135.0–140.3) | 0.7 ± 2.9 (1.0–2.3) | 0.39    |          |
| Time, h |     |            |                 |            |          |          |
| 0      | 7   | 138.6 ± 2.4 (136.3–140.8) | 135.1 ± 5.0 (130.5–139.8) | 3.4 ± 3.6 (0.1–6.7) | 0.04    |          |
| 1      | 7   | 138.6 ± 2.4 (136.3–140.8) | 137.0 ± 3.1 (134.2–138.9) | 1.6 ± 1.9 (0.2–3.3) | 0.07    |          |
| 2      | 7   | 138.6 ± 2.4 (136.3–140.8) | 137.6 ± 3.2 (134.7–140.5) | 2.7 ± 1.0 (1.5–3.5) | 0.36    |          |
| 3      | 7   | 138.6 ± 2.4 (136.3–140.8) | 137.6 ± 3.1 (134.7–140.4) | 1.9 ± 0.7 (0.8–2.8) | 0.22    |          |
| 4      | 7   | 138.6 ± 2.4 (136.3–140.8) | 137.9 ± 3.2 (134.9–140.8) | 0.7 ± 2.2 (1.3–2.8) | 0.43    |          |

*P* values refer to comparison between set and measured sodium with a paired t-test.

*P* value refers to comparison of differences in set and measured sodium with groups (e.g., sodium bath 135 versus sodium bath 140).

All values expressed as mean ± SD (95% confidence intervals) in mmol/l.

**Discussion**

Prescribed dialysate sodium is delivered by accurate proportioning of concentrates in the purified water by dialysis machines using constant analysis of dialysate conductivity. Conductivity, the result of the dissociation of electrically charged inorganic salts (releasing sodium, chloride, bicarbonate, magnesium, and calcium), in the dialysate solution is easily measured in real time using simple electrodes. Sodium and, to a much smaller extent, bicarbonate are the only parameters that vary significantly in dialysate, as the others are present in small quantities and at relatively fixed concentrations. Thus, conductivity measurements provide a close correlation with sodium concentration. Measured or delivered dialysate sodium is usually measured using standard biochemical analyzers.

In this study, we found that prescribed dialysate sodium measured via conductivity of dialysis machines was accurate when compared to a calibrated external
conductivity meter. However, we did find significant bias between prescribed and measured dialysate sodium concentration when dialysate sodium was measured using the plasma mode (which is the standard mode) of a standard biochemical analyzer, using ISE. These findings are in keeping with those previously reported by Gul et al. Importantly, this discrepancy was much smaller and likely to be clinically meaningless when the sodium level was measured using the same analyzer set to urine mode. We propose that the larger bias is apparent only with laboratory analyzers set to plasma mode as a result of inherent proprietary correction factors programmed in indirect measurement laboratory analyzers to account for the 7% of solids in plasma. These correction factors are used because the ISE method measures sodium activity rather than concentration (and sodium activity approaches sodium concentration in protein- and glucose-free aqueous solution). However, as dialysate contains no solid component, using the urine mode for analysis of dialysate sample is likely more accurate. This issue should affect only ISE electrodes, which rely on dilutions and calibration correction for solids. Because ISEs are by far the most common types of instruments used in the modern laboratory, these findings are important when interpreting dialysate sodium measurements.

Variability of the apparent bias between set and measured dialysate sodium based on the laboratory analyzer mode has, to our knowledge, never been reported and it is possible that previous reports of this bias may not have accounted for laboratory analyzer mode. The strengths of this study include that we selected 3 dialysis machines commonly used worldwide, tested on different dialysate sodium and potassium concentrations over the entire 4-hour patient-free dialysis session, with measurements performed on the 2 analyzer modes available. To minimize confounding that could have contributed to conductivity in addition to sodium, we created 3K acid concentrate by spiking 2K acid concentrate with KCL, thus preserving identical ionic concentration otherwise. We measured sodium concentration by the ISE method, which makes our analysis easily replicable. The limitations include a smaller sample size for measurements analyzed on the urine mode analyzer.

As there are multiple studies reporting on the relation between dialysate sodium and clinical outcomes, our findings shed some light on the notion that an unrecognized bias may have affected the results. With an ongoing large pragmatic sodium dialysate trial underway, our findings support that the set dialysate sodium does correspond to the delivered dialysate sodium when measurement techniques are accounted for and may help strengthen the relationship between dialysate sodium modulations and clinical outcomes.

In summary, we demonstrate a statistically significant, clinically meaningful bias between measured dialysate sodium compared to prescribed dialysate sodium when the laboratory analyzer is set to plasma mode. We demonstrate a much smaller and clinically irrelevant bias with the same analyzer set to urine mode. We suggest that when dialysate sodium is measured via ISE, analyzers should be set to urine mode. Even with this, it is likely that a small 1- to 2-mmol/l bias will be observed, but explained by the inherent proprieties of ISE.

**DISCLOSURE**

All the authors declared no competing interests.

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**AUTHOR CONTRIBUTIONS**

SH, PAB, EGC, and CM had a significant role in conception and design of the work that led to the submission, acquired data, and played an important role in interpreting the results, and drafted and revised the manuscript. RS acquired data, played an important role in interpreting the results, and drafted and revised the manuscript. AA had a significant role in conception and design of the work that led to the submission. RS, SH, EGC, AA, CM, and PAB approved the final version of this manuscript. PAB has had full access to the data in the study and final responsibility for the decision to submit for publication.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)
Supplementary Methods.
Supplementary References.

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